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REVIEW

Role of endoplasmic reticulum stress in drug-induced toxicity

Fabienne Foufelle[1] & Bernard Fromenty[2]

[1]INSERM, UMRS 1138, Centre de Recherche des Cordeliers, Paris, France
[2]INSERM, UMR 991, Université de Rennes 1, Rennes, France

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Correspondence
Bernard Fromenty, Fromenty, INSERM UMR 991, Faculté de Pharmacie, 2 avenue du Professeur Léon Bernard, 35043 Rennes Cedex, France. Tel: +33 2 23 23 30 44; Fax: +33 2 23 23 53 85; E-mail: bernard.fromenty@inserm.fr

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Abstract

Drug-induced toxicity is a key issue for public health because some side effects can be severe and life-threatening. These adverse effects can also be a major concern for the pharmaceutical companies since significant toxicity can lead to the interruption of clinical trials, or the withdrawal of the incriminated drugs from the market. Recent studies suggested that endoplasmic reticulum (ER) stress could be an important event involved in drug liability, in addition to other key mechanisms such as mitochondrial dysfunction and oxidative stress. Indeed, drug-induced ER stress could lead to several deleterious effects within cells and tissues including accumulation of lipids, cell death, cytolysis, and inflammation. After recalling important information regarding drug-induced adverse reactions and ER stress in diverse pathophysiological situations, this review summarizes the main data pertaining to drug-induced ER stress and its potential involvement in different adverse effects. Drugs presented in this review are for instance acetaminophen (APAP), arsenic trioxide and other anti-cancer drugs, diclofenac, and different antiretroviral compounds. We also included data on tunicamycin (an antibiotic not used in human medicine because of its toxicity) and thapsigargin (a toxic compound of the Mediterranean plant *Thapsia garganica*) since both molecules are commonly used as prototypical toxins to induce ER stress in cellular and animal models.

Abbreviations

APAP, acetaminophen; CHOP, C/EBP homologous protein; COX, cyclooxygenase; CYP, cytochrome P450; ER, endoplasmic reticulum; GI, gastrointestinal; GRP, glucose-related protein 78; GSH, glutathione; NAPQI, N-acetyl-*p*-benzoquinone imine; NRTI, nucleoside reverse transcriptase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; 4-PBA, 4-phenylbutyrate; PERK, PKR-like ER kinase; PI, protease inhibitor; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding protein; UPR, unfolded protein response.

Introduction

Drug-induced toxicity is an important issue for public health and the well-being of patients. Indeed, some side effects can be severe and require a hospitalization, or even can cause the death of some patients. These adverse effects can also be a major concern for the pharmaceutical companies because significant toxicity can lead to the interruption of clinical trials, or the withdrawal of the incriminated drugs from the market (Labbe et al. 2008; Elangbam 2010). In the recent years, the endoplasmic reticulum (ER) stress emerged as a potential important event involved in drug liability, in addition to other key mechanisms such as mitochondrial dysfunction and oxidative stress. Thus, the main objective of the present review was to collect the available information regarding drug-induced ER stress and its potential role in the occurrence of different adverse reactions. For this purpose, we performed a PubMed search of literature published in the English language using the following queries

(by alphabetical order): adverse effect, adverse event, adverse reaction, drug, drug-induced, ER stress, and toxicity. This data mining was also completed by using Google Scholar®. Besides the different drugs presented below, we also included data on tunicamycin and thapsigargin since both molecules are commonly used as prototypical toxins to induce ER stress in cellular and animal models.

Drug-Induced Adverse Effects and Main Mechanisms of Toxicity

Many drugs of our modern pharmacopeia are able to induce adverse effects that can involve different tissues such as the liver, heart, kidney, lung, skeletal muscles, adipose tissue, and peripheral nerves (Marrer and Dieterle 2010; Begriche et al. 2011; Hohenegger 2012; Tocchetti et al. 2013; Miltenburg and Boogerd 2014). Notably, a single drug can damage several tissues in the same patient and induce several types of lesions in a given tissue. For instance, drug-induced liver injury includes hepatic cytolysis, autoimmune-like hepatitis, cholestasis, steatosis, steatohepatitis, cirrhosis, and hepatocellular adenoma (Wang et al. 2013a; Leise et al. 2014). This variety of liver lesions actually reflects the occurrence of different mechanisms of toxicity and the potential involvement of several types of hepatic cells such as hepatocytes, cholangiocytes, stellate cells, activated lymphocytes, and Kupffer cells (Stirnimann et al. 2010; Czaja 2011; Padda et al. 2011).

It is currently acknowledged that mitochondrial dysfunction and oxidative stress are two major mechanisms whereby drugs can induce injuries in different tissues such as the liver, heart, and kidney (Sardao et al. 2008; John and Herzenberg 2009; Baillie and Rettie 2011; Begriche et al. 2011; Deavall et al. 2012; Tocchetti et al. 2013; Miltenburg and Boogerd 2014). Actually, drugs can induce oxidative stress via several mechanisms including by increasing reactive oxygen species (ROS) production by the dysfunctional mitochondria and higher NADPH oxidase activity and by reducing cellular antioxidant defenses (Labbe et al. 2008; Baillie and Rettie 2011; Begriche et al. 2011; Leung et al. 2012).

Drugs can be harmful either directly or indirectly after their biotransformation into one or several toxic reactive metabolites by cellular enzymes such as cytochromes P450 (CYPs) (Baillie and Rettie 2011; Begriche et al. 2011; Leung et al. 2012). Importantly, CYPs and other xenobiotic metabolizing enzymes (XMEs) are expressed mainly in the liver but also in other tissues including the gastrointestinal (GI) tract, kidney, lung, brain, heart, and white adipose tissue (Dutheil et al. 2009; Thelen and Dressman 2009; Ellero et al. 2010; Knights et al. 2013; Ravindranath and Strobel 2013). Hence, the generation of toxic reactive metabolites can occur in liver and extrahepatic tissues (Gu et al. 2005; Ding and Kaminsky 2003). Finally, besides mitochondrial dysfunction and oxidative stress, there is increasing evidence that ER stress can be another important mechanism in drug-induced adverse effects, as underlined in this review.

Definition and Cellular Consequences of ER Stress

The ER plays a crucial role in the synthesis of all the proteins that are secreted from cells, or inserted into organelle membranes. Efficient protein folding in the ER requires a tight coupling between the arrival of new proteins in the ER lumen and the ER folding capacity. Efficient folding requires ER-resident proteins such as chaperones and foldases that are calcium-binding/buffering proteins (Coe and Michalak 2009; Halperin et al. 2014). These proteins include for instance calreticulin, glucose-regulated protein 78 (GRP78, also known as immunoglobulin-binding protein or BiP), GRP94, and protein disulfide isomerase (PDI). When the demand for protein folding increases (e.g., enhanced protein synthesis, accumulation of mutated, or abnormal proteins, etc) and exceeds protein folding capacity, misfolded/unfolded proteins accumulate in the ER lumen and trigger an ER stress. Many physiological or pathological situations can interfere with protein folding and can thus impact ER homeostasis such as alterations of ER luminal calcium stores, energy depletion, redox disturbances, glucose starvation, lipid accumulation, viruses, ethanol intoxication, and xenobiotics (Malhi and Kaufman 2011; Cnop et al. 2012; Cheng et al. 2013; Chen et al. 2014). Notably, ER stress is leading to the activation of the so-called unfolded protein response (UPR), the role of which is to maintain protein homeostasis by decreasing the load of unfolded proteins and increasing the protein folding capacity (Fig. 1). In addition, ER stress is also able to activate autophagy- and proteasome-dependent proteolysis when misfolded proteins are in excess (Hoyer-Hansen and Jäättelä 2007; Digaleh et al. 2013).

UPR activation involves three different effectors (also referred to as the 3 arms of the UPR): inositol requiring 1α (IRE1α), PKR-like ER kinase (PERK), and activating transcription factor-6α (ATF6α) (Cawley et al. 2011; Dara et al. 2011; Malhi and Kaufman 2011). One of the main consequences of UPR activation is the inhibition of translation, in order to curb the synthesis of new proteins. This response is mediated by the kinase PERK that phosphorylates the alpha subunit of eukaryotic translation-initiation factor 2 (eIF2α) leading to a rapid reduction in the initiation of mRNA translation and thus reducing the load of new client proteins in the ER (Fig. 1).

Despite protein synthesis attenuation during ER stress, there is a small subset of genes that are specifically

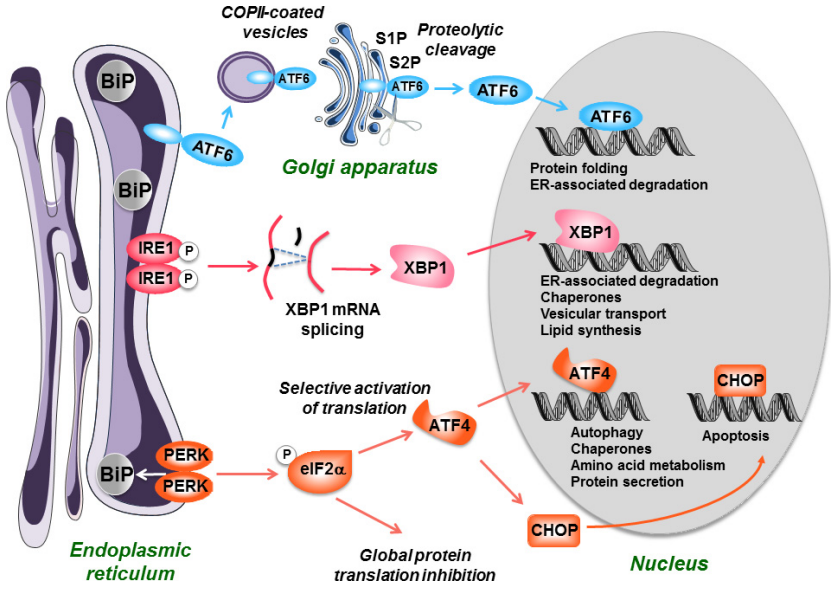

Figure 1. The unfolded protein response (UPR). When an endoplasmic reticulum (ER) stress occurs, the cell initiates an adaptive response called the UPR. It starts with the activation of three effectors, PKR-like ER kinase (PERK), IRE1, and ATF6, following the removal of the chaperone BiP (GRP78) that maintains them in an inactivated state. PERK is a kinase which phosphorylates and inactivates the elongation initiation factor eIF2α, leading to a general decrease in protein translation. However, eIF2α selectively stimulates the translation of ATF4, a transcription factor which possesses a specific structure (uORF) on its mRNA. ATF4 then activates the synthesis of chaperones and proteins involved in autophagy, protein secretion, and amino acid metabolism. IRE1 possesses a kinase activity leading to its autophosphorylation and activation of a RNAse activity. This leads to the splicing of XBP1 mRNA, which is then translated into an active transcription factor. The transcription factor ATF6, which is bound to the ER membranes as an inactive precursor is transferred via COPII-coated vesicles to the Golgi apparatus, where it is cleaved by the S1P and S2P proteases into an active form. XBP1 and ATF6 will then activate in the nucleus the transcription of a set of factors allowing to restore ER homeostasis including chaperones, foldases, and proteins involved in the degradation of unfolded polypeptides (ER-associated degradation). If these mechanisms are not efficient to restore ER and cell homeostasis, the UPR will eventually activate mechanisms leading to cell apoptosis, in particular via the transcription factor C/EBP homologous protein (CHOP).

transcribed and translated via the three branches of the UPR (Fig. 1). For instance, these genes encode ER-associated degradation (ERAD) proteins, ER chaperones (BiP/GRP78 and GRP94), and enzymes able to expand protein folding capacity including PDI and foldases (Kaufman 1999; Dara et al. 2011). This physiological response is also called the adaptive UPR. In contrast, if the UPR is strong enough and/or sustained, some deleterious consequences can be observed such as apoptosis, which can be dependent or not of mitochondria (Hom et al. 2007; Deniaud et al. 2008; Malhi and Kaufman 2011; Sano and Reed 2013). Importantly, the mitochondrial-independent pathway of apoptosis triggered by ER stress is the consequence of the activation of different specific effectors such as the transcription factor C/EBP homologous protein (CHOP, also referred to as GADD153) and caspase 12 (Malhi and Kaufman 2011; Sano and Reed 2013). Depending of the stressors, caspase 12 activation can require the translocation of caspase 7 from the cytosol to the ER membranes, or a calcium-mediated recruitment of calpain to the ER surface (Nakagawa and Yuan 2000; Rao et al. 2001; Xie et al. 2002).

Another consequence of ER stress in some cells can be the stimulation of lipid synthesis by activation of different transcription factors such as sterol regulatory element-binding proteins (SREBPs), CAAT/enhancer-binding proteins (C/EBP) and peroxisome proliferator-activated receptor-γ (PPARγ) (Werstuck et al. 2001; Colgan et al. 2007; Malhi and Kaufman 2011; Lee et al. 2012). It is also important to point out that ER stress and impaired protein folding can lead to the production of a significant amount of ROS (Malhotra and Kaufman 2007; Malhotra et al. 2008). Interestingly, it is estimated that 25% of the ROS generated in a cell results from the formation of disulfide bonds in the ER during normal protein synthesis (Tu and Weissman 2004; Sevier and Kaiser 2008). Conversely, ROS accumulation can induce the oxidation of resident ER proteins, including proteins of the polypeptide folding machinery such as PDI and BiP (van der Vlies et al. 2002, 2003), thus leading to an ER stress and creating a vicious cycle (Malhotra and Kaufman 2007). To alleviate the deleterious effects of ROS, the PERK branch of the UPR can activate the transcription of several key antioxidant enzymes via the phosphorylation

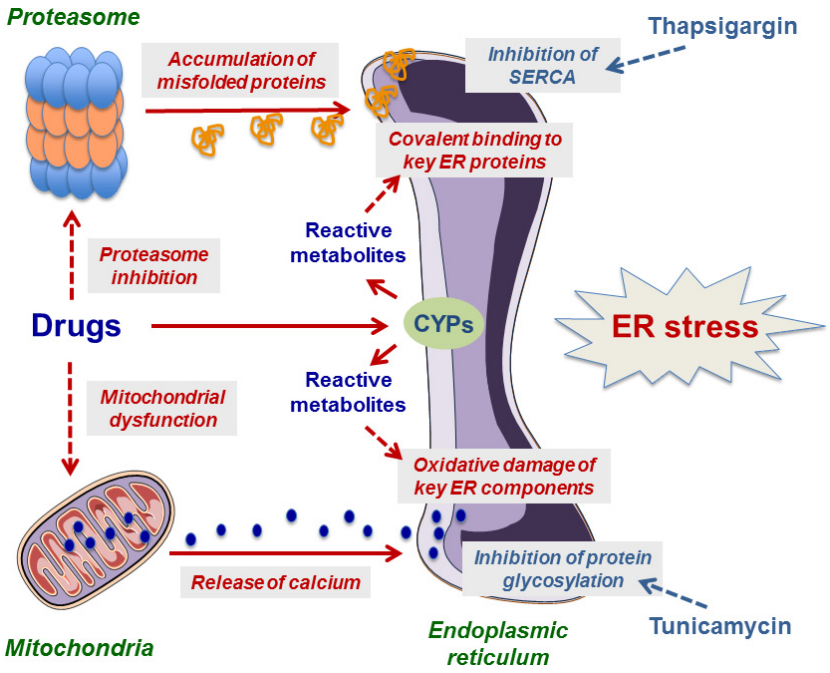

Figure 2. Potential mechanisms of drug-induced endoplasmic reticulum (ER) stress. Drugs are able to induce ER stress via different mechanisms including proteasome inhibition, mitochondrial dysfunction, and alteration of key ER components. The latter mechanism is suspected with drugs that are transformed into one or several reactive metabolites able to bind covalently to ER proteins and/or to induce oxidative damage of ER components secondary to oxidative stress. Cytochromes P450 (CYPs) are often involved in the generation of reactive metabolites. The figure also indicates the respective targets of thapsigargin and tunicamycin, which are two prototypical inducers of ER stress. Further information is provided in the text and Table 1.

of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (Cullinan and Diehl 2006; Flamment et al. 2012).

Drug-Induced ER Stress and Adverse Effects

Acetaminophen (APAP)

APAP is a popular drug for the management of pain and hyperthermia (Table 1). Although APAP is usually deemed as a safe drug, APAP intoxication after an overdose can lead to massive hepatocellular necrosis and acute liver failure (Craig et al. 2011). Moreover, there is evidence that the maximum recommended dose (i.e., 4 g/day) can induce mild to moderate hepatic cytolysis, even in healthy individuals (Watkins et al. 2006; Winnike et al. 2010). APAP can also induce acute kidney injury in some patients, either after poisoning or at therapeutic doses (Blakely and McDonald 1995; Kato et al. 2014). APAP-induced acute nephrotoxicity manifests as acute tubular necrosis with oliguric renal failure, which can occur alone or in association with liver injury (Blakely and McDonald 1995; Jones and Prescott 1997). APAP overdose has also been reported to induce cardiotoxicity, pancreatitis, and ototoxicity (Jones and Prescott 1997; Yorgason et al. 2011).

APAP is mainly metabolized in the liver into the nontoxic glucuronide and sulfate conjugates. However, a small amount of APAP is oxidized to the reactive metabolite N-acetyl-*p*-benzoquinone imine (NAPQI) by CYPs 2E1 (CYP2E1) and 3A4 (Gonzalez 2007; Aubert et al. 2012). After its generation, NAPQI is normally detoxified by glutathione (GSH) when APAP is taken at the recommended dosage. After APAP overdose, or in the presence of predisposing factors, high levels of NAPQI can induce cytotoxicity. Indeed, once GSH is deeply depleted and no longer available for NAPQI detoxication, this reactive metabolite binds to different proteins, in particular at the mitochondrial level (Michaut et al. 2014). This is followed by profound mitochondrial dysfunction and ATP depletion, overproduction of ROS, c-jun N-terminal kinase (JNK) activation, and massive hepatocellular necrosis (Jaeschke et al. 2012; Michaut et al. 2014). APAP-induced acute nephrotoxicity could also involve CYP2E1-mediated generation of NAPQI, depletion of GSH, and secondary oxidative stress (Hart et al. 1994; Das et al. 2010).

In vivo and *in vitro* investigations reported that APAP was also able to induce an ER stress and that such deleterious effect could play an significant role in APAP-induced cell death in liver, kidney, or inner ear (Lorz et al. 2004; Nagy et al. 2007, 2010; Uzi et al. 2013; Kalinec et al. 2014). In one of these studies, mortality

Table 1. Drugs for which adverse events have been linked to ER stress.

Drug(s)	Pharmacological class	Main side effects	Mechanism of ER stress	Additional information
Acetaminophen (APAP)	Antalgic and antipyretic	Hepatotoxicity and nephrotoxicity, commonly after an overdose	Currently unknown. Possible involvement of the APAP-derived reactive metabolite NAPQI, which binds to several key microsomal proteins including PDI and calreticulin	ER stress could be a late event after APAP intoxication, compared to other deleterious events such as mitochondrial dysfunction and oxidative stress
Amiodarone	Antiarrhythmic and antianginal	Hypotension, cutaneous reactions, thyroid toxicity, liver injury, and pulmonary toxicity	Currently unknown	ER stress could be involved in some amiodarone-induced adverse effects (e.g., thyroid and lung toxicity) in addition to mitochondrial dysfunction
Arsenic trioxide (As_2O_3)	Anticancer agent used to treat acute promyelocytic leukemia and other hematologic malignancies	GI disorders, rash, hematologic toxicity, infections, cardiac toxicity renal toxicity, myopathy, neuropathy, and hepatotoxicity	Possible involvement of oxidative stress and impairment of protein folding	In addition to ER stress, mitochondrial dysfunction is also likely to be involved in the pathogenesis of some adverse effects induced by arsenic trioxide
Bleomycin	Anticancer drug used in different malignancies such as lymphomas, head and neck cancers as well as ovarian and testicular cancers	GI disorders, cutaneous reactions, myelosuppression, and life-threatening pulmonary toxicity	Currently unknown. Possible mechanisms could involve oxidative stress	ER stress could be involved in bleomycin-induced pulmonary toxicity
Bortezomib (PS-341)	Anticancer drug used to treat multiple myeloma and mantle cell lymphoma	GI symptoms, fatigue, peripheral neuropathy, and thrombocytopenia	Proteasome inhibition	ER stress is one mechanism whereby bortezomib is able to induced apoptosis in cancer cells. ER stress could be involved in bortezomib-induced peripheral neuropathy
Cisplatin	Anticancer drug used in various malignancies such as testicular, gastric, lung, breast, and ovarian cancers	GI disorders, kidney injury, neurotoxicity, hepatotoxicity, and cardiotoxicity	Currently unknown. Possible mechanisms could involve oxidative stress and/or the covalent binding of cisplatin to key microsomal proteins	ER stress could be involved in cisplatin-induced kidney injury
Clozapine and olanzapine	Antipsychotics	GI disorders, drowsiness, extrapyramidal symptoms, elevation in liver enzymes, and obesity (with related metabolic disorders such as insulin resistance and fatty liver)	Currently unknown. Possible involvement of increased cytosolic calcium	Although fatty liver induced by clozapine and olanzapine could be secondary to obesity, hepatocyte ER stress directly induced by these drugs might also be involved
Cyclosporin	Immunosuppressant	Infections, hypertension, neurotoxicity, nephrotoxicity, and hepatotoxicity (including cholestasis and cytolysis)	Currently unknown. In hepatocytes, a possible mechanism could be the covalent binding of cyclosporin metabolites to pivotal microsomal proteins	Possible involvement of ER stress in cyclosporin-induced cholestasis. Cyclosporin-induced ER stress in kidney could be indirect consequence of vascular dysfunction
Diclofenac	NSAID	GI complications (including gastric injury and intestinal damage), hypersensitivity	Currently unknown. Possible involvement of increased intracellular calcium in	Possible involvement of ER stress in diclofenac-induced

(*Continued*)

Table 1. Continued.

Drug(s)	Pharmacological class	Main side effects	Mechanism of ER stress	Additional information
		reactions, hepatotoxicity, and kidney injury	gastric mucosal cells. Because diclofenac metabolism generates two *p*-benzoquinone imines similar to APAP-derived NAPQI, binding to key ER proteins could be involved (in liver and other tissues expressing CYPs)	GI complications and liver toxicity
Efavirenz	Antiretroviral (non-nucleoside reverse transcriptase inhibitor)	Rash, neuropsychological symptoms, lipodystrophy, and hepatotoxicity (in particular cytolysis and cholestasis)	Possible secondary consequence of mitochondrial dysfunction and release of mitochondrial calcium into the cytosol	Possible involvement of ER stress in efavirenz-induced hepatotoxicity
Erlotinib	Anticancer drug used in different malignancies including non-small cell lung cancer and pancreatic cancer	Rash and GI manifestations (in particular severe diarrhea)	Currently unknown	Possible involvement of ER stress in erlotinib-induced small intestinal injury and diarrhea
Furosemide	Diuretic used to treat hypertension and edema	Dehydration, hypotension, hyponatremia, and hypokalemia	Currently unknown	Hepatic ER stress has been detected in mice treated by furosemide. Extrapolation to humans is doubtful since this drug induces virtually no hepatotoxicity in patients
Indomethacin	NSAID	GI complications (including gastric injury and intestinal damage), hypersensitivity reactions, hepatotoxicity, and kidney injury	Currently unknown. Possible involvement of increased intracellular calcium (in gastric mucosal cells)	Possible involvement of ER stress in indomethacin-induced GI complications and liver toxicity
Paclitaxel (Taxol)	Anticancer agent used in different malignancies including ovarian, breast, and lung cancers	GI disorders, cardiac and skeletal muscle toxicity, myelosuppression, neurotoxicity, and acute liver injury (mostly hepatic cytolysis)	Currently unknown	Possible involvement of ER stress in paclitaxel-induced neurotoxicity
Protease inhibitors (e.g., indinavir and ritonavir)	Antiretroviral	GI toxicity, rash, kidney injury, hepatotoxicity (including cytolysis, cholestasis, and steatosis), dyslipidemia, lipodystrophy, insulin resistance, and type 2 diabetes	Possible involvement of proteasome inhibition and oxidative stress	Significant ER stress has been showed with atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, but not with amprenavir, darunavir, and tipranavir
Sertraline	Antidepressant (selective serotonin reuptake inhibitor)	Somnolence, GI disorders, tremor, sexual dysfunction, weight gain, and liver injury	Currently unknown. Possible role of mitogen-activated protein kinase (MAPK) pathway activation	Possible involvement of ER stress in sertraline-induced hepatotoxicity
Thapsigargin	Sesquiterpene lactone isolated from the plant *Thapsia garganica*, which has long been used in traditional Arabian medicine	Severe skin irritation, salivary hypersecretion, gastroenteritis, nervous disorders, and death	Inhibition of SERCA, thus leading to severe calcium depletion in the ER	Prototypical inducer of ER stress. In addition to ER stress, increase in free cytosolic calcium is inducing apoptosis in different types of cells treated with thapsigargin

(*Continued*)

Table 1. Continued.

Drug(s)	Pharmacological class	Main side effects	Mechanism of ER stress	Additional information
Troglitazone	Antidiabetic (via activation of PPARγ)	Severe and fatal liver injury leading to the withdrawal of troglitazone from the market	Currently unknown. Possible role of mitogen-activated protein kinase (MAPK) pathway activation	Possible involvement in troglitazone-induced liver injury in addition with mitochondrial dysfunction and oxidative stress
Tunicamycin	Antibiotic active against different bacteria, fungi, and viruses	Major neurotoxicity and death in animals. Kidney and liver lesions are also observed in the treated animals	Impairment of glycosylation of newly synthesized proteins in the ER leading to the disruption of their folding	Prototypical inducer of ER stress. Tunicamycin has never been used in human medicine due to its toxicity
Zidovudine (AZT)	Antiretroviral (nucleoside reverse transcriptase inhibitor)	Lactic acidosis, myopathy, and hepatotoxicity (including cytolysis and steatosis)	Currently unknown. Possible impairment of proteasome activity	Although ER stress could be involved in steatosis, the current knowledge points to a major role of mitochondrial dysfunction in fat accretion induced by zidovudine

ER, endoplasmic reticulum; CYPs, cytochromes P450; GI, gastrointestinal; PDI, protein disulfide isomerase; NAPQI, N-acetyl-*p*-benzoquinone imine; NSAID, nonsteroidal anti-inflammatory drug; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; PPARγ, peroxisome proliferator-activated receptor-γ.

induced by a lethal dose of APAP (1 g/kg) was completely prevented in CHOP knockout mice but data regarding liver injury induced by a lower dose of this painkiller (500 mg/kg) showed either a protection or no effect depending of the route of APAP administration (Uzi et al. 2013). In addition, other studies dealing with APAP hepatotoxicity did not find markers of ER stress (Van Summeren et al. 2011; Hur et al. 2012; van Summeren et al. 2013). Actually, some data in mice indicated that ER stress was a relatively late event after APAP intoxication (500 mg/kg), being significant only 12 hours following APAP administration (Hur et al. 2012; Uzi et al. 2013). In contrast, mitochondrial alterations, ATP depletion, JNK activation, oxidative stress, and increased cytosolic calcium occurred much earlier in mouse liver after the same dose of APAP (Burcham and Harman 1988; Jaeschke 1990; Ruepp et al. 2002; Aubert et al. 2012; Hur et al. 2012). Investigations in the human hepatoma HuH7 cell line also suggested that ER stress induced by APAP occurred well after mitochondrial alterations (Macanas-Pirard et al. 2005). Thus, further studies are required to determine whether ER stress is a major pathway involved in APAP toxicity and cell death.

The mechanism whereby APAP induces ER stress is poorly understood. A first hypothesis could be the occurrence of microsomal alterations secondary to NAPQI generation. Indeed, it has been reported that APAP induced severe GSH depletion, lipid peroxidation, and an oxidative shift of the ER oxidoreductases ERp72 and PDI in liver microsomes (Nagy et al. 2007; Letelier et al. 2011). Furthermore, NAPQI can covalently bind to several microsomal proteins such as GSH-S-transferase, PDI, and calreticulin (Pumford et al. 1990; Weis et al. 1992; Zhou et al. 1996; Shin et al. 2007). Because PDI and calreticulin play a major role in protein folding and calcium sequestration within the ER (Coe and Michalak 2009), covalent binding of NAPQI to these proteins could induce an ER stress. Interestingly, it has been shown that other reactive benzoquinones induced an ER stress (Wang et al. 2006). Second, ER stress might also be a secondary consequence of mitochondrial dysfunction, as discussed later on with other drugs such as arsenic trioxide and efavirenz.

Amiodarone

This broad-spectrum antiarrhythmic drug also presents an antianginal effect (Table 1). The main adverse effects of amiodarone include hypotension, thyroid toxicity (hyper- or hypothyroidism), pulmonary toxicity including bronchiolitis and pulmonary fibrosis, and hepatic lesions such as steatosis, steatohepatitis, and cirrhosis (Dusman et al. 1990; Fromenty and Pessayre 1995; Santangeli et al. 2012). Numerous studies have shown that mitochondrial dysfunction is a major mechanism of amiodarone-induced toxicity in liver and other tissues (Fromenty and Pessayre 1995; Di Matola et al. 2000; Nicolescu et al. 2008; Begriche et al. 2011). Recently, amiodarone was shown to induce ER stress in thyrocytes and lung epithelial cells (Mahavadi et al. 2014; Lombardi et al. 2015), but the involved mechanism was not determined in these

studies. In contrast, no ER stress was detected in hepatocytes treated with amiodarone, although it was observed with cyclosporin A in the same investigations (Van Summeren et al. 2011; van Summeren et al. 2013).

Arsenic Trioxide

Arsenic trioxide (As_2O_3) is used as an effective anticancer drug for the treatment of acute promyelocytic leukemia (APL) (Table 1). Interestingly, arsenic trioxide can be effective in APL patients refractory to all-trans retinoic acid and other conventional anticancer drugs such as anthracyclines (Shen et al. 1997; Breccia and Lo-Coco 2012). This compound could also be useful in other hematologic malignancies such as multiple myeloma and myelodysplastic syndromes, although higher doses are needed in these diseases (Douer and Tallman 2005; Xu et al. 2014). As_2O_3 exerts its powerful therapeutic effect in APL by promoting the degradation of a specific oncogenic protein, the so-called PML-RARα fusion protein (Emadi and Gore 2010; Zhang et al. 2010). In contrast, regarding the other hematologic malignancies, this drug could be effective by activating several pathways leading to cancer cell apoptosis including mitochondrial dysfunction, oxidative stress, and DNA damage (Pelicano et al. 2003; Emadi and Gore 2010; Kumar et al. 2014; Xu et al. 2014). Notably, some of these effects could be the consequence of a direct interaction of arsenic trioxide with GSH and protein thiols (Scott et al. 1993; Hughes 2002; Lu et al. 2007; Zhang et al. 2010). Some studies also suggested that ER stress could be involved in the anticancer action of arsenic trioxide (Du et al. 2006; Chen et al. 2012; Chiu et al. 2015).

As_2O_3 can induce different adverse effects including GI disorders, rash, hematologic toxicity (e.g., thrombocytopenia and neutropenia), infections, cardiac and renal toxicity, myopathy, neuropathy, and hepatotoxicity (Douer and Tallman 2005; Schiller et al. 2006; Echaniz-Laguna et al. 2012). Some of these side effects can be serious and even fatal in a few cases (Westervelt et al. 2001; Schiller et al. 2006). It is also noteworthy that chronic arsenic poisoning via contaminated water and food is also associated with a wide array of deleterious effects, which overlap with arsenic trioxide toxicity (Yoshida et al. 2004; Emadi and Gore 2010). Unsurprisingly, investigations in noncancerous cells and in rodents suggested that some of these side effects could be secondary to oxidative stress and mitochondrial dysfunction (Aposhian and Aposhian 2006; Jomova et al. 2011; Mathews et al. 2013; Garcia-Sevillano et al. 2014; Vineetha et al. 2015). Several studies also showed that arsenic trioxide triggered ER stress in different types of nonmalignant cells such as myoblasts, vascular endothelial cells, pancreatic β-cells, neutrophils, and macrophages (Binet et al. 2010; Lu et al. 2011; Yen et al. 2012; Srivastava et al. 2013; Weng et al. 2014; King et al. 2015). In several of these studies, ER stress was associated with other deleterious events including loss of the mitochondrial membrane potential, increased intracellular free calcium, ROS overproduction, and apoptosis (Lu et al. 2011; Yen et al. 2012; Srivastava et al. 2013; Weng et al. 2014; King et al. 2015). Interestingly, arsenic trioxide-induced ER stress could be prevented by the GSH precursor N-acetylcysteine (Lu et al. 2011; Yen et al. 2012; Srivastava et al. 2013; King et al. 2015), or by the mitochondrial-targeted antioxidant tiron (Weng et al. 2014). Since arsenic trioxide has been shown to increase mitochondrial ROS production possibly via an impairment of the respiratory chain (Paul et al. 2008; Vineetha et al. 2015), ROS released from mitochondria could thus play a significant role in arsenic trioxide-induced ER stress. However, arsenic trioxide might also directly induce ER stress because some authors showed with in vitro assays that this compound was able to impair protein folding (Ramadan et al. 2009; Jacobson et al. 2012).

Bleomycin

This anticancer drug is used to treat several types of malignancies such as lymphomas, head, and neck cancers as well as ovarian and testicular cancers (Table 1). Bleomycin induces oxidative DNA damage and subsequent cell death after formation of a complex with iron (or copper) and oxygen, which generates free radicals able to create DNA single- and double-strand breaks (Hecht 2000; Chen and Stubbe 2005). Notably, this drug is also able to oxidatively damage other cellular targets such as RNA, proteins, and lipids (Chen and Stubbe 2005). Bleomycin-induced adverse effects include GI disorders, myelosuppression, cutaneous reactions, and pulmonary toxicity, in particular severe and life-threatening lung fibrosis (Froudarakis et al. 2013; Della Latta et al. 2015). The pathophysiology of bleomycin lung toxicity seems complex, but could involve oxidative stress, inflammation, and overproduction of profibrotic cytokine transforming growth factor-β (TGFβ) (Chen and Stubbe 2005; Kikuchi et al. 2011; Froudarakis et al. 2013; Della Latta et al. 2015). Recent investigations suggested that ER stress could also be involved (Zhao et al. 2014a,b; Tanaka et al. 2015). In one of these studies, bleomycin-induced lung fibrosis was significantly reduced in $CHOP^{-/-}$ mice (Tanaka et al. 2015). Although the mechanism of bleomycin-induced ER stress was not determined in these investigations, it is conceivable that oxidative damage of key ER components could be involved. In this regard, previous studies reported that N-acetylcysteine was able to alleviate

bleomycin-induced lung injury (Hagiwara et al. 2000; Serrano-Mollar et al. 2003; Kikuchi et al. 2011).

Bortezomib

This anticancer drug is approved for the treatment of several types of cancers including multiple myeloma and mantle cell lymphoma (Table 1). The mechanism of action of bortezomib (also known as PS-341) involves the specific inhibition of proteasome, which is responsible for cytotoxicity and apoptosis in cancer cells (Holkova and Grant 2012; Dou and Zonder 2014). Indeed, proteasome inhibition secondarily leads to ER stress, ROS production, and activation of JNK and other signaling pathways inducing cell death (Lee et al. 2003; Fribley et al. 2004; Holkova and Grant 2012). The most frequent adverse events with this drug are GI symptoms, peripheral neuropathy, fatigue, and thrombocytopenia (Holkova and Grant 2012; Argyriou et al. 2014). One study suggested that bortezomib-induced ER stress could be involved in peripheral neuropathy, possibly by impairing myelin synthesis (Shin et al. 2010).

Cisplatin

Cisplatin, also known as cisplatinum or cis-diamminedichloroplatinum (II) (CDDP), is an antitumor agent used to treat various malignancies including testicular, gastric, lung, breast, and ovarian cancers (Table 1). Although the formation of cisplatin-DNA adducts is deemed to be a key mechanism leading to cancer cell apoptosis, other mechanisms independent of DNA damage could also be involved such as ROS overproduction, increased plasma membrane fluidity, and ER stress (Mandic et al. 2003; Maccio and Madeddu 2013; Dasari and Tchounwou 2014).

Cisplatin treatment can induce several types of adverse effects including GI disorders, kidney injury, neurotoxicity, hepatotoxicity, and cardiotoxicity (Kitamura 2008; Pabla and Dong 2008; Florea and Büsselberg 2011). Many investigations have been performed to decipher the mechanisms of cisplatin-induced acute kidney injury because this frequent adverse effect limits the use of cisplatin in cancer therapy (Kitamura 2008; Pabla and Dong 2008). The emerging picture to explain cisplatin-induced tubular cell injury and death is a combination of different pathophysiological events including mitochondrial dysfunction, ROS overproduction, increased tumor necrosis factor-α (TNFα) generation, and ER stress (Kruidering et al. 1997; Kitamura 2008; Pabla and Dong 2008; Servais et al. 2008; Mukhopadhyay et al. 2012). Indeed, markers of ER stress such as increased BiP/GRP78 and CHOP expression and caspase 12 activation have been found in different investigations performed in renal cells and kidneys of rodents treated with cisplatin (Liu and Baliga 2005; Peyrou et al. 2007; Khan et al. 2013; Kong et al. 2013; Gao et al. 2014; Wang et al. 2014; Chen et al. 2015). Interestingly, kidneys of CHOP$^{-/-}$ mice showed less evidence of cell death when treated with cisplatin (Zinszner et al. 1998). Despite these investigations, the precise mechanism(s) whereby cisplatin is able to induce ER stress is still unknown. Possible hypotheses could be cisplatin-induced oxidative stress and/or irreversible binding of this drug to key ER components. In this regard, cisplatin has been shown to covalently bind to different proteins, including in the microsomal compartment (Pattanaik et al. 1992; Litterst and Schweitzer 1988; Huliciak et al. 2012).

Clozapine and olanzapine

These antipsychotic drugs are structurally similar to the sedative and anxiolytic benzodiazepines (Table 1). The antipsychotic action of clozapine and olanzapine is deemed to be due to dopamine D2 receptor blockade, although interactions with other neurotransmitter receptors have been reported (Reynolds and Kirk 2010; Brosda et al. 2014). The most common adverse effects of these compounds include GI manifestations, drowsiness, extrapyramidal symptoms, cardiac effects, elevation of liver enzymes, and obesity, which can be associated with insulin resistance and fatty liver (Melkersson and Dahl 2003; Begriche et al. 2011; De Fazio et al. 2015; Rojo et al. 2015). Although clozapine- and olanzapine-induced fatty liver could be secondary to obesity, investigations in human hepatocytes also suggested a role of ER stress, SREBP1c activation and increased hepatic lipogenesis, possibly via a calcium-dependent pathway (Lauressergues et al. 2012). Another study showed that olanzapine induced ER stress and reduced insulin secretion in hamster pancreatic β cells (Ozasa et al. 2013). However, the pathophysiological significance of this effect remains unclear since this drug classically induces hyperinsulinemia, even in the absence of weight gain (Melkersson and Dahl 2003; Teff et al. 2013).

Cyclosporin

Cyclosporin (also known as cyclosporin A) is a potent immunosuppressant isolated from the fungus *Tolypocladium inflatum* (Table 1). This drug significantly improves the short-term transplant survival by reducing the incidence of acute allograft rejection. Like tacrolimus (FK506), cyclosporin exerts its immunosuppressive effect by inhibiting calcineurin, thus impairing the activation of the nuclear factor of activated T cells (NFAT) signaling pathway that plays a major role in T-cell-mediated

adaptive immune response (Graham 1994; Jorgensen et al. 2003). Unfortunately, cyclosporin treatment can induce numerous side effects, which are sometimes severe and require the discontinuation of the treatment. Besides infections (that are the direct consequence of immunosuppression), cyclosporin can also induce hypertension, neurotoxicity (e.g., paresthesia and tremor), nephrotoxicity, and hepatotoxicity (Krupp and Monka 1990; Graham 1994; Servais et al. 2008). Liver toxicity not only includes cholestasis but also hepatic cytolysis and steatosis (Biour et al. 2004; Wang et al. 2013a).

Cyclosporin is extensively metabolized in liver and kidney by several CYPs, which generate at least 30 different metabolites (Kelly et al. 1999; Zheng et al. 2013). Some of these metabolites are able to form stable adducts with cellular proteins indicating that they are highly reactive in nature (Nagelkerke et al. 1987; Sadrieh and Thomas 1994; Christians and Sewing 1995). Notably, oxidative stress seems to be an important mechanism whereby cyclosporin can lead to cytolysis in different cell types (Wolf et al. 1997; Nishida et al. 2003; Navarro-Antolin et al. 2007) and to kidney or liver damage in treated rodents (Tariq et al. 1999; Kaya et al. 2008; Haleagrahara et al. 2009). Cyclosporin-induced oxidative stress could be the consequence of mitochondrial dysfunction and reduced antioxidant defenses (Kaya et al. 2008; Palomero et al. 2001; Redondo-Horcajo et al. 2010; Xiao et al. 2013).

Several studies carried out in mouse hepatocytes and the human hepatoma cell lines HepG2 and HepaRG showed that cyclosporin was able to induce an ER stress (Van Summeren et al. 2011; van Summeren et al. 2013; Szalowska et al. 2013; van den Hof et al. 2014; Sharanek et al. 2014). Interestingly, the investigations performed in HepaRG cells showed that reduced canalicular efflux of taurocholate induced by high concentrations (50 μmol/L) of cyclosporin were alleviated by 4-phenylbutyrate (4-PBA), a chemical chaperone commonly used to protect against ER stress (Sharanek et al. 2014). However, lower concentrations of cyclosporin (10 μM) impaired taurocholate canalicular efflux without inducing ER stress (Sharanek et al. 2014). Notably, several studies showed that cyclosporin is a potent inhibitor of the bile salt export pump (BSEP) (Dawson et al. 2012; Pedersen et al. 2013). Thus, these investigations suggest that cyclosporin-induced impairment of bile acid efflux and cholestasis could be secondary to ER stress only for high concentrations of this immunosuppressant. Whether ER stress plays a role in cyclosporin-induced hepatic cytolysis and steatosis has not been addressed in the aforementioned studies. Moreover, it is still unknown how cyclosporin can induce ER stress in liver. A first mechanism could involve CYP-mediated generation of reactive metabolites able to alter key ER proteins since some of these metabolites can bind covalently to microsomal proteins (Nagelkerke et al. 1987; Sadrieh and Thomas 1994). Another mechanism might be the occurrence of oxidative stress and lipid peroxidation within the ER (Barth et al. 1991; Serino et al. 1993).

Different *in vitro* and *in vivo* investigations also attempted to determine whether ER stress could be an important mechanism involved in cyclosporin-induced nephrotoxicity (Han et al. 2008; Pallet et al. 2008; Lhotak et al. 2012; Sarro et al. 2012; Liu et al. 2015). These studies performed in cultured renal proximal tubule cells and kidneys of treated rats clearly showed that this immunosuppressant agent was able to induce an ER stress (e.g., activation of CHOP, BiP/GRP78, and GRP94). In addition, markers of ER stress have been found in renal biopsies of patients with cyclosporin-induced acute or chronic nephrotoxicity (Lhotak et al. 2012; Hama et al. 2013). However, despite these data, a direct causal relationship between cyclosporin-induced ER stress and nephrotoxicity is doubtful. Indeed, numerous experimental and clinical studies provided strong evidence that cyclosporin-induced nephrotoxicity is mainly the consequence of reduced renal blood flow due to afferent and efferent arteriolar vasoconstriction (English et al. 1987; Kon et al. 1990; Smith et al. 1992; Grieve et al. 1993; Pannu and Nadim 2008). Since hypoxia can induce an ER stress in particular in the kidney (Inagi et al. 2014; Suh et al. 2014), renal ER stress observed during cyclosporin nephrotoxicity could be a mere consequence of vascular dysfunction induced by this drug. Finally, it is noteworthy that cyclosporin is not able to bind covalently to microsomal proteins in kidney, contrary to what happens in liver microsomes (Nagelkerke et al. 1987; Sadrieh and Thomas 1994).

Diclofenac and indomethacin

The nonsteroidal anti-inflammatory drugs (NSAIDs) diclofenac and indomethacin are discussed together because of their similar pharmacological and toxicological profiles (Table 1). Indeed, these drugs are potent nonselective inhibitors of the cyclooxygenases 1 and 2 (COX1 and COX2) used for the treatment of chronic inflammatory diseases such as osteoarthritis and rheumatoid arthritis. As many other nonselective COX inhibitors, the most significant side effects induced by diclofenac and indomethacin are GI complications such as bleeding and ulceration, hypersensitivity reactions (e.g., anaphylaxis, skin eruptions, and bronchospasms), and kidney injury (Rossi et al. 1985; Richy et al. 2004; Gonzalez et al. 2009; Castellsague et al. 2012; Wallace 2012). These drugs can also induce hepatotoxicity, mostly cytolytic hepatitis and cholestasis (Banks et al. 1995; Biour et al. 2004; Wang et al. 2013a).

The most common NSAID-induced GI toxicity seems to be gastric injury, albeit intestinal damage could also be a frequent side effect observed in treated patients (Wallace 2012; Boelsterli et al. 2013). Numerous studies have shown that a major mechanism of NSAID-induced gastropathy is COX inhibition and the secondary decreased production of mucosal prostaglandins, which have a major cytoprotective action on the gastric mucosa (Rainsford and Willis 1982; Wallace 2012; Seminerio et al. 2014). Nevertheless, some investigations suggested that ER stress could also be involved for some NSAIDs including diclofenac and indomethacin (Tsutsumi et al. 2004; Ohyama et al. 2012). In one of these studies, indomethacin-induced apoptosis in guinea-pig gastric mucosal cells was partially but significantly prevented by expression of a dominant-negative form of CHOP (Tsutsumi et al. 2004). One mechanism whereby some NSAIDs are able to induce ER stress and apoptosis in gastric mucosal cells could be an increase in intracellular calcium levels secondary to membrane permeabilization (Tanaka et al. 2005).

Contrary to NSAID-induced gastropathy, COX inhibition does not seem to play a primary role in NSAID-induced enteropathy, although decreased prostaglandin synthesis could render the intestine more susceptible to injury. Indeed, oxidative stress, mitochondrial dysfunction, and TNFα release could be important mechanisms in NSAID enteropathy (Wallace 2012; Boelsterli et al. 2013). Recent investigations carried out in rat intestinal slices suggested that diclofenac could be toxic via an ER stress in addition to mitochondrial injury and oxidative stress (Niu et al. 2014). ER stress was also observed in cultured rat enterocytes treated with indomethacin (Narabayashi et al. 2015).

An important mechanism of diclofenac-induced hepatocellular injury is the CYP-mediated generation of two *p*-benzoquinone imines and possibly other reactive metabolites triggering oxidative stress, mitochondrial dysfunction, and cell death (Bort et al. 1999; Boelsterli 2003; Park et al. 2005). In addition, diclofenac is able to induce direct mitochondrial dysfunction (Begriche et al. 2011; Porceddu et al. 2012; Massart et al. 2013). Although ER stress with CHOP induction has been observed in hepatic cells treated with diclofenac (Franceschelli et al. 2011; Nadanaciva et al. 2013; Fredriksson et al. 2014), it is still unclear whether this event plays a primary role in diclofenac-induced cell demise, compared to mitochondrial dysfunction. Moreover, the mechanism whereby diclofenac induces ER stress in hepatocytes is still unknown. Although diclofenac was shown to bind irreversibly to hepatic microsomal proteins in several studies (Kretz-Rommel and Boelsterli 1994; Hargus et al. 1995; Obach et al. 2008), the targeted polypeptides are still unidentified. It will be interesting to determine whether diclofenac-derived *p*-benzoquinone imines can bind covalently to the microsomal PDI and calreticulin, as does APAP-derived NAPQI (Zhou et al. 1996). Finally, it is noteworthy that indomethacin was also found to induce ER stress in hepatic cells (Franceschelli et al. 2011). However, similar to diclofenac, it is still unclear whether ER stress is the primary mechanism of liver injury induced by indomethacin since this drug is also able to directly impair mitochondrial function (Jacob et al. 2001; Porceddu et al. 2012).

Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase inhibitors (NNRTIs) used to treat the human immunodeficiency virus (HIV) infection (Table 1). Efavirenz can induce several types of side effects including neuropsychological manifestations (e.g., dizziness, headache, and depression), rash, lipodystrophy and hepatotoxicity, which can occur as hepatic cytolysis and cholestasis (Sulkowski et al. 2002; Biour et al. 2004; Maggiolo 2009; Margolis et al. 2014). Several studies also suggest that efavirenz could trigger endothelial dysfunction and increase the cardiovascular risk in HIV-infected patients (Maggi et al. 2011; Gupta et al. 2012). The exact mechanism whereby efavirenz can be toxic is still unclear. Several studies showed that efavirenz can induce mitochondrial dysfunction in different experimental models including human hepatic cells (Apostolova et al. 2010; Blas-García et al. 2010), primary rat neurons (Purnell and Fox 2014) and different brain regions of treated mice (Streck et al. 2011). A recent study reported that efavirenz was able to induce an ER stress in human hepatic Hep3B cells, with an upregulation of CHOP, BiP/GRP78, and phospho-eIF2α (Apostolova et al. 2013). However, investigations demonstrated that this deleterious effect was actually secondary to mitochondrial dysfunction and the release of mitochondrial calcium into the cytosol (Apostolova et al. 2013). Two recent studies also showed that efavirenz-induced ER stress in human endothelial cells (Bertrand and Toborek 2015; Weiß et al. 2015), but the involved mechanism was not determined in these investigations.

Protease inhibitors

Protease inhibitors (PIs) are antiretroviral drugs frequently used for the treatment of HIV-infected patients (Table 1). This important pharmacological class includes numerous compounds such as amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. Taken as a whole, these drugs can

induce GI toxicity such as nausea and diarrhea, rash, liver and kidney injury, dyslipidemia, lipodystrophy, insulin resistance, and type 2 diabetes (Gougeon et al. 2004; Pannu and Nadim 2008; Izzedine et al. 2009; Caron-Debarle et al. 2010; Margolis et al. 2014). As regards hepatotoxicity, different types of lesions have been described in treated patients such as cytolysis, cholestasis, steatosis, and cirrhosis (Biour et al. 2004; Wang et al. 2013a). Some PIs such as indinavir, lopinavir, and ritonavir are suspected to increase the risk of cardiovascular diseases including myocardial infarction (Bavinger et al. 2013; Margolis et al. 2014).

PIs are toxic via different pathways, in particular by inducing mitochondrial dysfunction and oxidative stress and by promoting inflammation (Gougeon et al. 2004; Caron et al. 2007; Caron-Debarle et al. 2010; Mencarelli et al. 2012; Bociaga-Jasik et al. 2013; Cassol et al. 2013; Reyskens et al. 2013). Several studies also reported that some PIs are able to induce ER stress in different types of cells (e.g., macrophages, adipocytes, hepatocytes) and tissues (e.g., liver, intestine) (Zhou et al. 2005; Gupta et al. 2007; Cao et al. 2010; Touzet and Philips 2010; Wu et al. 2010; Zha et al. 2010, 2013; Brüning 2011; Zhou 2011; Brüning et al. 2012; Apostolova et al. 2013; Taura et al. 2013; Wang et al. 2013b). In these investigations, ER stress was consistently observed with atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir. In contrast, amprenavir, darunavir, and tipranavir induced only a weak or no ER stress in the different tested experimental models (Wu et al. 2010; Zhou 2011; Taura et al. 2013; Zha et al. 2013). Notably, some of these studies brought evidence that PI-induced ER stress was involved in lipid metabolism alterations, inflammation, cell apoptosis, and tissue damage, in particular by using $CHOP^{-/-}$ mice or cells (Zhou et al. 2005; Cao et al. 2010; Wu et al. 2010; Zha et al. 2010, 2013; Zhou 2011; Wang et al. 2013b). According to these investigations, ER stress could thus be an important mechanism whereby some PIs are able to induce metabolic disturbances such as lipodystrophy, hepatic steatosis and cytolysis, dyslipidemia, and some cardiovascular complications. Lastly, it is noteworthy that PI-induced ER stress and hepatocyte damage have been shown to be potentiated by ethanol exposure (Kao et al. 2012; Hu et al. 2015). Interestingly, one of these studies reported that the combination of PIs and ethanol significantly induced ER stress and cell death in mouse hepatocytes but not in mouse Kupffer and stellate cells (Hu et al. 2015). These experimental data could be clinically relevant because previous investigations reported a greater risk of PI-induced severe hepatic injury in patients abusing alcohol (Nunez et al. 2001).

The precise mechanisms whereby some PIs can induce ER stress is still unclear, although two hypotheses have been proposed. The first mechanism could be PI-induced inhibition of proteasome activity (Parker et al. 2005; Pyrko et al. 2007; Bono et al. 2012). Indeed, several studies carried out with other compounds (e.g., bortezomib) showed that specific impairment of proteasome function can potently trigger ER stress (Lee et al. 2003; Fribley et al. 2004; Bono et al. 2012). In this context, ER stress occurs because the proteasome cannot degrade the few misfolded proteins that are normally but constantly produced within the ER (Fribley and Wang 2006; Xu et al. 2005). Proteasome inhibition has been shown for atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, although the potency of this inhibitory effect seemed variable between these drugs (Schmidtke et al. 1999; Pajonk et al. 2002; Piccinini et al. 2002; Parker et al. 2005; Bono et al. 2012). The second potential mechanism could involve PI-induced oxidative stress, as suggested by some investigations (Touzet and Philips 2010; Taura et al. 2013). However, the precise origin of oxidative stress has not been addressed in these studies.

Thapsigargin

This sesquiterpene lactone of the Mediterranean plant *Thapsia garganica* is a prototypical and powerful inducer of ER stress (Zinszner et al. 1998; Rutkowski et al. 2008; Kammoun et al. 2009) (Table 1). More precisely, thapsigargin induces ER stress by inhibiting sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) (Fig. 2), thus leading to severe depletion of ER calcium (Kaufman 1999; Denmeade and Isaacs 2005; Schönthal 2012). In addition to ER stress-induced activation of downstream effectors that can trigger cell death, the concomitant increase in free cytosolic calcium is also a potent proapoptotic signal in different types of cells (Jiang et al. 1994; Treiman et al. 1998; Kim et al. 2008). In mast cells, thapsigargin-induced augmentation in cytosolic calcium is leading to the release of histamine, which could explain the potent skin irritating effects of *Thapsia garganica* (Jacobsen et al. 1987; Doan et al. 2015). Other toxic effects of this plant can include salivary hypersecretion, gastroenteritis, vomiting and diarrhea, nervous disorders, fever, and death in the most severe cases of intoxication (Bnouham et al. 2006; Hammiche et al. 2013). Despite its significant toxicity, *Thapsia garganica* has long been used in traditional Arabian medicine for the treatment of different illnesses including rheumatic pains, women infertility, and pulmonary diseases (Treiman et al. 1998; Bnouham et al. 2006; Hammiche et al. 2013). In the past few years, different thapsigargin analogs have been developed as potential drug candidates for the treatment of prostate cancers (Isaacs 2005; Dubois et al. 2013; Doan et al. 2015).

Tunicamycin

This glucosamine-containing antibiotic produced by *Streptomyces lysosuperificus* is active against different types of microorganisms including gram-positive bacteria, fungi, yeast, and viruses (Table 1). Early investigations have demonstrated that this antibiotic was able to inhibit the synthesis of N-glycoproteins in yeast and bacteria (Kuo and Lampen 1974; Bettinger and Young 1975) as well as in animals and plants (Fig. 2) (Takatsuki and Tamura 1971; Tkacz and Lampen 1975; Ericson et al. 1977). More specifically, tunicamycin impairs the transfer of N-glucosamine to the polyisoprenoid lipid dolichol phosphate, the first step in the synthesis of the lipid-linked oligosaccharide that is used as a precursor for the N-glycoproteins (Ericson et al. 1977; Bieberich 2014). Notably, this biosynthetic step takes place within the ER in eukaryotic cells (Bieberich 2014). Consequently, impairment of glycosylation of newly synthesized proteins is leading to the disruption of their folding in the ER (Kaufman 1999; Schönthal 2012). In addition, this alteration of peptide conformation can secondarily prevent the cellular secretion of some proteins such as different immunoglobulins (Hickman et al. 1977; Elbein 1981).

Tunicamycin has never been used in human medicine because of its major toxicity. In particular, acute tunicamycin administration in rodent, cattle and sheep is leading to severe neurotoxicity with disturbed consciousness, convulsions, and paralysis, which can occasionally lead to the death of the treated animals (Leaver et al. 1988; Bourke and Carrigan 1993). The lesions in the brain are mainly vascular and it is deemed that blood vessel damage could secondary lead to brain ischemia and hypoxic neuronal damage (Finnie and O'Shea 1988; Leaver et al. 1988). Indeed, tunicamycin damages the endothelial cells of small blood vessels with marked dilatation of the rough ER (i.e., typical of the presence of ER stress), which appears to strongly distort their cytoplasm and cause stenosis of the blood vessel lumen (Finnie and O'Shea 1988; Finnie and O'Shea 1990a). Tunicamycin-induced direct endothelial toxicity has also been observed *in vitro* in vascular endothelial cells (Finnie and O'Shea 1990a; Galan et al. 2014; Suganya et al. 2014). Nevertheless, *in vitro* studies also showed that tunicamycin can induce neuronal cell death in different types of neurons (Chang and Korolev 1996; Kosuge et al. 2006; Galehdar et al. 2010). Some of these *in vitro* investigations demonstrated that tunicamycin-induced endothelial and neuronal cell death was linked to ER stress (Kosuge et al. 2006; Galehdar et al. 2010; Suganya et al. 2014).

In addition to its neurotoxicity, tunicamycin is also able to induce acute liver and kidney injuries in the intoxicated animals (Zinszner et al. 1998; Finnie and O'Shea 1989; Finnie and O'Shea 1990b; Marciniak et al. 2004; Rutkowski et al. 2008; Carlisle et al. 2014). Notably, tunicamycin-induced acute kidney injury is blunted in CHOP knockout mice, or in mice treated with the chemical chaperone 4-PBA (Marciniak et al. 2004; Carlisle et al. 2014). In liver, the lesions observed in tunicamycin-intoxicated animals include steatosis, bile ductular hyperplasia, swollen hepatocytes, and the presence of apoptotic bodies (Finnie and O'Shea 1989; Finnie and O'Shea 1990b; Finnie et al. 2004; Rutkowski et al. 2008). Interestingly, swollen hepatocytes are characterized by a marked dilatation of the rough ER (Finnie and O'Shea 1989; Finnie et al. 2004). The precise mechanism of tunicamycin-induced hepatic steatosis is still elusive. Although some data suggested that tunicamycin could favor *de novo* lipogenesis in particular via a SREBP1c-dependent pathway (Kammoun et al. 2009; Lee et al. 2012), other investigations did not support this mechanism (Rutkowski et al. 2008; Jo et al. 2013). Alternatively, tunicamycin could favor intrahepatic lipid accumulation by other mechanisms including reduced expression and activity of the transcription factor PPARα, a master regulator of fatty acid oxidation (Rutkowski et al. 2008; Yamamoto et al. 2010; Chikka et al. 2013), impairment of triglyceride excretion (Zhang et al. 2011), or increased lipid delivery to the liver (Jo et al. 2013; Bogdanovic et al. 2015).

Zidovudine

This nucleoside reverse transcriptase inhibitor (NRTI) is the first antiretroviral drug marketed for the treatment of HIV (Table 1). Other NRTIs include stavudine (d4T), lamivudine (3TC), didanosine (ddI), and tenofovir. Despite their pharmacological interest, these drugs can unfortunately induce a large array of side effects, which are sometimes fatal, such as hepatotoxicity, renal dysfunction, myopathy, pancreatitis, peripheral neuropathy, lipodystrophy, and lactic acidosis (Izzedine et al. 2009; Caron-Debarle et al. 2010; Begriche et al. 2011; Margolis et al. 2014). NRTI-induced liver injury includes hepatic cytolysis, microvesicular and/or macrovacuolar steatosis, steatohepatitis, and cirrhosis (Biour et al. 2004; Massart et al. 2013; Wang et al. 2013a). Numerous investigations have shown that the main mechanism involved in NRTI toxicity is mitochondrial dysfunction, as these drugs can reduce mitochondrial DNA (mtDNA) levels in various tissues via DNA polymerase γ inhibition (Gaou et al. 2001; Igoudjil et al. 2006; Schon and Fromenty 2016). A recent study showed that zidovudine-induced hepatic steatosis in mice was associated with an ER stress, with a concomitant increase in SREBP1c expression and reduced

PPARα expression (Banerjee et al. 2013). However, mtDNA levels and mitochondrial function were not measured in this study and thus it remains unclear whether zidovudine-induced ER stress was the main mechanism of fat accumulation in mouse liver. In addition, the mechanism whereby zidovudine could induce an ER stress is still unknown, although a previous study showed that this drug was able to significantly inhibit the proteasome activity (Piccinini et al. 2002).

Other drugs

The antidepressant sertraline and the antidiabetic troglitazone can be toxic for the liver (Table 1) (Biour et al. 2004; Wang et al. 2013a). Importantly, troglitazone caused several cases of fatal liver failure and was thus withdrawn from the market (Labbe et al. 2008). The role and mechanisms of ER stress in sertraline and troglitazone-induced hepatotoxicity have been discussed in a recent review (Chen et al. 2014). Hepatic ER stress has also been detected in a mouse model of liver toxicity induced by the diuretic drug furosemide (Table 1) (Qu et al. 2014). However, extrapolation of these experimental data to humans is doubtful because furosemide induces virtually no hepatotoxicity in treated patients (Biour et al. 2004; McGill et al. 2015).

Erlotinib is an anticancer drug that can induce severe diarrhea requiring an interruption of the treatment (Table 1) (Reck et al. 2011). A recent study provided some evidence that erlotinib-induced ER stress in rat small intestine epithelial cells was involved in apoptosis and reduced expression of E-cadherin (Fan et al. 2014). These effects might explain why erlotinib can impair the gut barrier integrity and induce diarrhea (Fan et al. 2014). ER stress could also be involved in the neuronal toxicity of the anticancer drug paclitaxel (Table 1) (Tanimukai et al. 2013), in addition to microtubule stabilization (Gornstein and Schwarz 2014).

Concluding Remarks and Remaining Issues

The present review underlines that ER stress could be involved in different adverse effects induced by drugs belonging to different pharmacological classes. However, it is still unclear whether ER stress is a common key pathophysiological signal involved in drug-induced toxicity. This may be because ER stress has not been frequently assessed in the context of drug-induced side effects, in contrast to other mechanisms of toxicity such as mitochondrial dysfunction and oxidative stress. It is also noteworthy that a great number of studies reported only a mere association between ER stress and cellular (or tissue) alterations. Hence, it is difficult to ascertain from these reports that ER stress is *bona fine* involved in drug-induced toxicity. In contrast, some of the aforementioned studies brought causal relationship by using $CHOP^{-/-}$ mice or cells (Zinszner et al. 1998; Marciniak et al. 2004; Wu et al. 2010; Zhou 2011; Uzi et al. 2013; Wang et al. 2013b; Zha et al. 2013; Tanaka et al. 2015). Thus, future investigations should use these experimental models, or similar ones with knockout of other major proteins involved in ER stress such as IRE1, PERK, or ATF6 (Fig. 1).

As previously mentioned, some investigators used 4-PBA in order to determine whether this chemical chaperone could alleviate drug-induced cellular (or tissue) damage. However, besides being protective against ER stress, 4-PBA presents other biological effects. For instance, 4-BPA was shown to be a histone deacetylase (HDAC) inhibitor and an autophagy inducer, to regulate Hsp70 expression and to present antioxidant and anti-inflammatory properties (Iannitti and Palmieri 2011; Suaud et al. 2011; Roy et al. 2012; Rekha et al. 2015). Thus, protection afforded by 4-BPA might not be fully related to ER stress defense.

In some studies, the presence of ER stress is based on the assessment of only a few UPR markers such as BiP/GRP78 and CHOP. However, accurate ER stress monitoring should include several markers activated by the three canonical arms of the UPR, as underscored in previous reviews (Samali et al. 2010; Cawley et al. 2011; Hiramatsu et al. 2011). Since the detection of cleaved ATF6, phospho-PERK, and phospho-IRE1 is rather difficult, different downstream targets of these three effectors can be studied (Samali et al. 2010). Hence, in addition to BiP/GRP78 and CHOP, other UPR markers should be investigated at the mRNA and/or protein level such as spliced X-box binding protein 1 (XBP1), homocysteine-inducible ER protein (HERP), ER degradation enhancer mannosidase alpha-like 1 (EDEM1), phospho-eIF2α, and ATF4 (Samali et al. 2010; Cawley et al. 2011; Hiramatsu et al. 2011). In addition, investigations on drug-induced ER stress should systematically include a positive control such as tunicamycin or thapsigargin.

It must be also pointed out that the exact mechanism of ER stress was not addressed in most of the studies cited in this review. In contrast, investigations performed with a few drugs suggested that ER stress could be secondary to oxidative stress (i.e., arsenic trioxide), proteasome inhibition (i.e., bortezomib), or increased cytosolic calcium (i.e., efavirenz) (Fig. 2). The data reported with efavirenz are particularly interesting because ER stress and elevated cytosolic calcium were found to be secondary to mitochondrial dysfunction (Apostolova et al. 2013). Notably, mitochondrial dysfunction induced by other factors including toxins can secondarily cause an augmentation in cytosolic calcium (Luo et al. 1997; Sheehan et al.

1997; Biswas et al. 1999; Amuthan et al. 2002). Since numerous drugs are able to impair mitochondrial function (Labbe et al. 2008; Begriche et al. 2011; Porceddu et al. 2012; Jones et al. 2014), it will be important to determine whether some of these drugs are also able to induce an ER stress by increasing cytosolic calcium.

Another mechanism of drug-induced ER stress that deserves to be carefully addressed is the covalent binding of reactive metabolites to ER proteins (Fig. 2). Indeed, drugs can be toxic because of their biotransformation by CYPs into one or several reactive metabolites, as previously discussed. Importantly, CYPs are mainly located in the ER membranes, although some CYPs could be also found in mitochondria (Avadhani et al. 2011; Knockaert et al. 2011). In addition, it is noteworthy that CYPs are expressed in various tissues, as previously mentioned. Thus, covalent binding of reactive metabolites to ER proteins could occur with some drugs in different tissues and might lead to ER stress and side effects.

Mitochondrial dysfunction can secondarily lead to ER stress, as previously mentioned. However, a reciprocal relationship has also been showed in some pathophysiological situations. For instance, ER stress induced by thapsigargin and tunicamycin can secondarily promote mitochondrial calcium accumulation and opening of the mitochondrial permeability transition (MPT) pore as well as other mitochondrial alterations leading to cell death (Hom et al. 2007; Deniaud et al. 2008). Actually, there is a close connection between ER and mitochondria and the physical association of the two organelles creates a structure known as the mitochondria-associated ER membrane (MAM) (Csordas et al. 2006; Hayashi et al. 2009). In the physiological context, this connection allows a constant transfer of calcium between ER and mitochondria (Csordas et al. 2010; Giacomello et al. 2010). During ER stress, calcium can be massively transferred to the mitochondria through these ER-mitochondria microdomains, or as a consequence of increased cytosolic calcium (Mandic et al. 2003; Benali-Furet et al. 2005; Deniaud et al. 2008; Timmins et al. 2009). Hence, induction of ER stress can secondarily augment the mitochondrial overload of calcium and thus favor mitochondrial membrane permeabilization and the release of proapoptotic factors such as cytochrome *c* and apoptosis-inducing factor (Deniaud et al. 2008; Pinton et al. 2008; Timmins et al. 2009; Fonseca et al. 2013). In the context of drug-induced toxicity, it will thus be important to gain more information regarding the relationship between ER stress and mitochondrial dysfunction and to determine whether some drugs can specifically interact with MAM. This may help to find strategies to prevent, or alleviate, some adverse effects that can be severe and life-threatening in some patients.

Disclosure

None declared.

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