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HIV protease inhibitors in gut barrier dysfunction and liver injury

Xudong Wu¹, Yunzhou Li², Kesong Peng³, and Huiping Zhou^{2,3,4}

¹State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing, Jiangsu, China, 210093

²McGuire Veterans Affairs Medical Center, Richmond, Virginia, 23249

³School of Pharmacy, Wenzhou Medical University, Wenzhou, Zhejiang, China, 325035

⁴Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond, Virginia, 23298.

Abstract

The development of HIV protease inhibitors (HIV PIs) has been one of the most significant advances of the past two decades in controlling HIV infection. HIV PIs have been used successfully in highly active anti-retroviral therapy (HAART) for HIV infection, which is currently the most effective treatment available. Incorporation of HIV PIs in HAART causes profound and sustained suppression of viral replication, significantly reduces the morbidity and mortality of HIV infection, and prolongs the lifespan of HIV patients. However, in the era of HAART, drug-induced gastrointestinal (GI) side effects and hepatotoxicity have emerged as important potential complications of HIV therapy, particularly those regimens containing HIV PIs. In this mini-review, we highlight the current understanding of the mechanisms of HIV PI-associated GI and liver injury.

Keywords

HAART; HIV protease inhibitor; ER stress; gastrointestinal injury; hepatotoxicity

Introduction

The acquired immunodeficiency syndrome (AIDS) epidemic has rapidly expanded since the discovery of the human immunodeficiency virus (HIV) as the cause of this disease in 1983. By the end of 2012, the estimated number of people living with HIV reached 35.3 million worldwide[1]. More than 25 million people have died of AIDS since 1981. Based on the most recent UNAIDS report, there were 2.3 (1.9–2.7) million new HIV infections globally in 2012, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million

Correspondence to: Dr. Huiping Zhou Department of Microbiology & Immunology Virginia Commonwealth University P.O. Box 980678, Richmond, VA 23298-0678 Tel: 804-828-6817; Fax: 804-828-0676 hzhou@vcu.edu.

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in 2001 [1]. And at the same time the number of AIDS deaths is also declining with 1.6 (1.4–1.9) million AIDS deaths in 2012, which is down from 2.3 (2.1–2.6) million in 2005. The decrease of HIV infection and AIDS death is often attributed to an increase of people receiving the life-saving antiretroviral therapy [1]. Antiretroviral therapy not only prevents AIDS-related illness and death, but it also has the potential to significantly reduce the risk of HIV transmission.

HIV is the most widely spread retrovirus in human. Understanding of the life cycle of HIV allows for the rapid development of specific anti-HIV drugs. Most anti-HIV drugs currently used in the clinic target the key steps in viral replication. The HIV protease is an enzyme that plays an essential role in HIV replication and the formation of infectious virus. HIV protease inhibitors (HIV PIs) block the maturation of HIV and cause formation of nonfunctional, immature, and noninfectious virions by selectively inhibiting HIV-1 and HIV-2 protease [2]. Since the incorporation of HIV PIs in highly active anti-retroviral therapy (HAART) in 1994, the morbidity and mortality of HIV infection have been significantly reduced and the lifespan of HIV patients have been markedly prolonged [2]. Despite the clinical successes of HIV PIs in controlling HIV replication, accumulating clinical evidence suggests that treatment with HIV PIs is associated with the occurrence of serious hepatic toxicities and GI complications, which are the common causes of treatment interruption or discontinuation of HAART [3,4]. During last two decades, a significant amount of effort has been put to identify the mechanisms underlying HIV PI-induced GI complications and hepatic lipotoxicity in HIV-infected patients. An increasing body of evidence suggests that multiple mechanisms may be involved and individual HIV PIs may have different effects on hepatic lipid metabolism and GI barrier function.

HIV protease inhibitors and HAART

Since the development of the first anti-HIV drug in 1987, more than two dozens of anti-HIV drugs have been approved by FDA. HAART, represents the most effective therapy to suppress HIV viral replication and the progression of HIV infection [5]. Combination of multiple drugs targeting different steps of HIV replication not only increases the therapeutic efficacy, but also reduces drug resistance and toxicities. The most commonly used HAART regimens are combinations of reverse transcriptase inhibitors, HIV PIs, or/and HIV integrase inhibitors.

HIV PIs are the core components of HAART. Two generations of HIV PIs have been developed since 1995. The first generation HIV PIs are structural analogues of the HIV Phe-Pro protease cleavage site and are classified as peptidomimetic inhibitors [6]. Eight HIV PIs (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir) in this class have been approved by the Food and Drug Administration (FDA) for the treatment of HIV infection. These drugs are selective, competitive, and reversible inhibitors of HIV-1 and HIV-2 protease, and they block the maturation of the virus and cause formation of nonfunctional, immature, and noninfectious virions. Atazanavir is an azapeptide protease inhibitor of HIV-1 protease that differs structurally from other approved peptidomimetic PIs by its C-2 symmetric chemical structure [7]. The second generation of HIV PIs is a class of non-peptidic HIV PIs. There are two HIV PIs (tipranavir and

darunavir) in this class that have been approved by the FDA. Tipranavir is active against HIV-1 strains that are resistant to other HIV PIs [8]. An increasing amount of clinical data indicate that HIV PIs are closely linked to various HAART-induced complications, especially diarrhea, dyslipidemia, hepatic lipotoxicity, and cardiovascular diseases [9-13].

HIV Protease Inhibitors and GI Barrier Dysfunction

HAART and diarrhea

Diarrhea is a common complication in HIV patients with HAART [13,14]. It was reported that acute diarrhea (≥ 3 bowel movements per day during the past 7 days) was observed in 28% of HIV-infected patients and in 92% of those receiving HAART, while only 7% of the HIV-seronegative controls showed symptoms of acute diarrhea [15]. Diarrhea adversely affects the life quality of HIV patients and is a major reason for discontinuing or switching HIV PI-based HAART regimens [16].

As a single-agent therapy, ritonavir is often associated with diarrhea (up to 1200 mg/d). Due to its serious side effects, ritonavir is currently only used as a pharmacokinetic booster to increase the concentrations of other PIs, including lopinavir, atazanavir, saquinavir, and darunavir [13,17]. Although a reduced dose of ritonavir is used in the booster combination, diarrhea remains as a common adverse effect depending on the choice of boosted PI [13]. In general, lopinavir/ritonavir and fosamprenavir/ritonavir tend to have the highest rates of drug-related diarrhea when compared with atazanavir/ritonavir, darunavir/ritonavir or saquinavir/ritonavir [18-20]. It is remarkable that all above ritonavir-boosted PI therapies are considered preferred or alternative first-line therapies for HIV infection.

Diarrhea and intestinal barrier function

Diarrhea may be acute or chronic. In addition to abnormal intestinal motility and malabsorption, diarrhea can be caused by either increased active intestinal ion secretion (secretory diarrhea) or by a leaky epithelial barrier (leak flux diarrhea). The intestinal epithelial layer represents the obvious physical boundary between the external and internal environment of the GI tract, and intestinal epithelial cells are the most integral part of its mucosal barrier [21]. The intercellular spaces between adjacent cells are connected together by junctional complexes (tight junctions and adherens junctions), which play a vital role in regulating the intestinal epithelial barrier. Tight junctions are composed of transmembrane proteins (claudins, occludins, and junctional adhesion molecules), peripheral membrane or scaffolding proteins (zonula occludens) and intracellular regulatory molecules [22,23]. Tight junctions are key determinants of mucosal barrier function and intestinal permeability, regulating the passage of solutes across the intestinal epithelium *via* the paracellular pathway [24]. Recently, there has been a renewed interest regarding the role of tight junctions in the pathophysiology of drug-induced gut toxicity [25]. The adherens junctions are composed of cadherins, forming immediately subjacent to the tight junctions [26]. Adherens junctions are important regulators of GI environment, as deletion of adherens junctions results in the disruption of epithelial polarization and differentiation and premature apoptosis of intestinal epithelial cells [26,27].

HIV PI-induced apoptosis and barrier dysfunction in intestinal epithelial cells via activation of ER stress

HIV PIs induce diarrhea *via* a variety of mechanisms, including increased calcium-dependent chloride conductance, cellular apoptosis and necrosis, and decreased proliferation of intestinal epithelial cells [28]. Braga Neto *et al* reported that HIV PIs disrupted intestinal barrier function and altered small intestinal absorption, which might contribute to HIV PI-associated diarrhea [29]. However, the underlying mechanism of HIV PI-induced disruption of intestinal barrier function remains unclear.

Our previous studies have already shown that HIV PIs induce ER stress, activate the unfolded protein response (UPR), and promote cell apoptosis in both macrophages and hepatocytes [30-32]. The ER is the principal site for protein synthesis and folding, calcium storage and signaling, and biosynthesis of corticosteroids, cholesterol, and other lipids. It is also highly sensitive to alterations in calcium homeostasis and perturbations in its environment. When triggered, the ER copes with the increased accumulation of unfolded or misfolded proteins by down-regulating protein synthesis and up-regulating the degradation pathway through UPR [33]. Three UPR transducers have been identified in mammalian cells including ER transmembrane kinase/endoribonuclease IRE1, doubled-stranded RNA-activated protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF-6). Activation of these ER stress transducers further induces the activation downstream transcription factors such as ATF4, X-box binding protein-1 (XBP-1) and C/EBP homologous protein (CHOP) [34]. CHOP is the major contributor to ER stress-induced apoptosis [35-37].

Similar to our findings in macrophages and hepatocytes, we also found that individual HIV PIs have differential effects on the UPR activation and apoptosis in normal intestinal epithelial cells (IECs). The most commonly used HIV PIs, ritonavir and lopinavir, significantly induced apoptosis and disrupted intestinal epithelial barrier integrity both *in vitro* and *in vivo*, whereas amprenavir had a lesser effect [38]. Lopinavir/ritonavir-induced dysfunction of intestinal epithelial barrier was greatly reduced in CHOP knockout mice [38]. Our recent studies also indicate that HIV PI-induced ER stress activation is correlated to the down-regulation of E-cadherin (E-cad) expression. As shown in Fig.1, lopinavir (LOPV), ritonavir (RITV), and thapsigargin (TG) significantly reduced mRNA levels and promoter activities of E-cad, but amprenavir, which does not induce ER stress, has no effect on E-cad mRNA expression and promoter activity. Therefore, HIV PI-induced ER stress and UPR activation represents an important cellular mechanism underlying HIV PI-induced intestinal epithelial barrier dysfunction. However, how HIV PIs induce ER stress in IECs remains to be further elucidated.

HIV Protease Inhibitors and Liver Injury

Hepatotoxicity is the common adverse effect of all US FDA-approved HIV PIs [39]. In dissecting out the direct effect of HIV PIs on liver injury, it has become apparent that individual HIV PIs have different effects, and there does not appear to be a single mechanism by which HIV PIs alter hepatic lipid metabolism and induce liver toxicity [39,40].

HIV PIs activate ER stress in hepatocytes

The liver plays a critical role in drug metabolisms. It is the most susceptible organ to drug-induced injury. Hepatocytes are the major player involved in lipid homeostasis, bile acid synthesis, gluconeogenesis, and drug metabolism. Therefore, disruption of normal cellular function of hepatocytes can lead to global physiological consequences. In HIV PI-induced metabolic dysfunctions, many features are similar to those observed in nonalcoholic fatty liver disease. HIV PIs have been clearly shown to alter lipid and carbohydrate metabolic pathways and cause insulin resistance [41,42].

The ER is a central player in regards to hepatic lipid metabolism. The sterol regulatory element-binding proteins (SREBPs), the major transcription factors involved in regulating hepatic lipid metabolism, reside in the ER membrane [43,44]. Our previous studies have shown that HIV PIs induced ER stress and increased the processing and activation of SREBPs in hepatocytes. Increased activation of SREBPs will increase the lipid accumulation in hepatocytes and ultimately induce hepatic lipotoxicity [30].

HIV PI-induced inflammatory response

Kupffer cells (KCs), the resident macrophages in the liver, are the largest population of mononuclear phagocytes in the body. KCs rapidly differentiate into mature macrophages in response various insults and play a significant role in control of inflammatory and immunologic processes in the liver. Activated KCs secrete various pro-inflammatory mediators such as cytokines and prostanoids and are known to be involved in the pathogenesis of various liver diseases [45]. Under normal physiological condition, KCs are exposed to low amount of gut-derived bacterial component (LPS), which is able to be cleared by KCs. However, under pathological conditions, such as inflammatory bowel diseases, drug-induced gut barrier dysfunction and systemic inflammation, KCs are activated to produce large amount of pro-inflammatory cytokines, such as TNF α , IL-1 β , and IL-6. It has been well-known that activation of inflammatory response promotes hepatic steatosis progression, fibrosis, and liver injury[46]. Our previous studies also reported that HIV PI-induced ER stress response directly increased the production of TNF α and IL-6 in macrophages [47]. Therefore, HIV PI-induced ER stress, intestinal barrier dysfunction, microbial translocation, and activation of inflammatory response represent important mechanisms underlying HAART-associated hepatic lipotoxicity.

Summary

HAART is the most effective treatment for HIV infection. HIV PI-induced GI side effects and hepatic injury are the major concerns of current HIV therapy. The burden of liver disease in AIDS is expected to increase as the number of patients living with HIV continues to rise. As illustrated in Fig.1, HIV PI-induced ER stress plays a critical role in HAART-associated GI complications and hepatic lipotoxicity. However, the underlying cellular and molecular mechanisms by which HIV PIs induce ER stress response remain to be fully elucidated. Therefore, a better understanding of the molecular mechanisms responsible for HIV PI-induced adverse effects might lead to the development of a new therapeutic strategy

that can reduce the incidence of GI complications, hepatic injury, and other related metabolic complications and improve the life quality of HIV patients under HAART.

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Highlights

- The current status of HIV infection and treatment.
- HIV protease inhibitors (PIs) induce side effects in GI tract *via* ER stress.
- HIV PIs induce inflammatory response via activation of ER stress.
- HIV PIs-induced ER stress and dysfunction of GI contribute to hepatic injury.

Fig. 1. Effect of HIV PIs on E-cadherin expression in IEC-6 cells

A. Effect of HIV PIs on mRNA levels in IEC-6 cells. Cells were treated with individual HIV PIs (25 μ M) for 24 h. The total cellular RNA was isolated and the E-cadherin mRNA levels were determined using real-time RT-PCR. Values are mean $\pm$ SE of three independent experiments. **B.** Effect of HIV PIs on E-cadherin promoter activity. IEC-6 cells were co-transfected with E-cadherin promoter luciferase reporter and pEGFP-C3 control vector for 24 h and then treated with individual HIV PIs (25 μ M) for 24 h. The reporter activity was measured 48 h after transfection. The transfection efficiency was normalized using GFP activity. Values are mean $\pm$ SD of three independent experiments. Thapsigargin (TG, 100 nM) was used as a ER stress positive control. * p <0.05, statistical significance relative to vehicle control, DMSO.

Fig. 2. Schematic diagram depicting the possible impact of HIV PI-induced ER stress on intestinal barrier function and hepatic lipid metabolism
HIV PI-induced ER stress disrupts intestinal barrier function and induces microbial translocation. HIV PI-induced ER stress not only directly disrupts hepatic lipid metabolism, but also activates Kupffer cells (KCs) and promotes the expression of pro-inflammatory cytokines, such as TNF- α and IL-6.