Journal of Clinical Trials
ISSN: 2167-0870

Ghose, J Clin Trials 2016, 6:1
DOI: 10.4172/2167-0870.1000e123

Editorial Open Access

Altered Expression/Activity of Cytochrome P450 (CYP) 3A4 Enzyme: Implications in Drug Safety and Efficacy

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Received date: January 27, 2016; **Accepted date:** January 29, 2016; **Published date:** February 05, 2016

Editorial

Cytochrome P450 (CYP) 3A4 enzyme alterations during diseases. Transcriptional or post-transcriptional down-regulation of hepatic CYP enzymes is a characteristic feature of many diseases including infections; cancer, cardiovascular diseases and liver disorders [1-5]. This disrupts CYP-mediated drug metabolism and clearance in these patients. The major drug metabolizing enzyme (DME) in human liver is CYP3A4, which metabolizes ~60% of drugs [6,7]. Recent studies in pediatric patients show that critical illness is the primary determinant of the clearance of the CYP3A4 substrate, midazolam [8]. Furthermore, diabetic kidney transplant patients had low metabolism of the immunosuppressant, cyclosporine A, likely due to reduced CYP3A4 expression [9]. These clinical observations warrant further studies to understand the molecular mechanism by which human CYP enzymes are down-regulated during diseases.

Role of CYP3A4 enzyme in herb-drug interactions. Furthermore, changes in CYP3A4 expression/activity has been shown to be associated with herb-drug interactions. According to recent epidemiological reports, ~40% of Americans use CAM "natural products" including herbal medicines, botanicals, and other dietary supplements during their lifetime [10-14]. These supplements are often self-administered primarily to manage side effects of drugs and/or to improve overall physical and mental health along with therapeutic drugs. Moreover, patients diagnosed with HIV or cancer exhibit a higher CAM use; concomitant use of CAM and prescription medications have been reported in 70%-90% HIV and cancer patients [15-17]. Natural products/herbs are complex mixtures of many molecular entities. Both the putative active ingredient(s) and other constituents present in that mixture have the potential to interact with various classes of drugs, which may lead to dangerous clinical consequences.

A majority of these interactions has been attributed to CYP3A4 enzyme. For example, the herbal compound St. John's wort induced CYP3A4, which decreased the oral bioavailability of a number of therapeutic drugs, including anti-depressants, anti-HIV agents, anti-cancer drugs, leading to failure of therapy [18-20]. Studies in animal models, humans or cell culture have shown that herbal compounds such as licorice, ginkgo, echinacea, quercetin, etc. significantly induced CYP3A expression/activity, leading to altered therapeutic potency of co-administered medications [16-20].

Regulation of CYP3A4 gene expression. Changes in CYP3A4 enzymes cause accumulation of the parent compound or the metabolite, which increases the risk of drug-drug interactions and adverse drug reactions (ADRs) in individual patients. A meta-analysis of 39 prospective studies revealed that ~2 million cases of hospitalization and ≥ 100,000 deaths/year can be attributed to ADRs in U.S.21 ADRs cause ~3%-6% of all hospital admissions and ~15% of hospitalized patients experience a serious adverse reaction to drugs [21-23]. Liver injury is one of the major adverse effects associated with drugs and accounts for ~50% of the cases of acute liver failure in this country [24].

Altered drug metabolism in diseases is associated with the induction of inflammatory responses. For example, CYP-mediated drug metabolism is disrupted and inflammatory markers are induced in patients undergoing treatment for several diseases including rheumatoid arthritis, cancer, organ transplantation, liver disorders [1-5]. Thus, treatment of rodents or liver cells with inflammatory mediators such as cytokines or lipopolysaccharide (LPS) has been widely used to investigate down-regulation of CYP enzymes in the liver [25-27].

CYP3A4 gene expression is regulated by basal transcription factors, and can be induced by diverse chemicals which bind to and activate nuclear receptors (NRs) [28,29]. The mouse xenobiotic NR, pregnane X receptor (PXR) is activated by the ligand, pregnenolone-16α-carbonitrile, PCN. Activated PXR binds to conserved sequences in the proximal promoter and the distal xenobiotic-responsive enhancer module (XREM) in the CYP3A4 gene [28,29]. The XREM is located -7.2 kb and -7.8 kb upstream of the transcription initiation site of CYP3A4. It contains PXR-responsive elements (PXREs) and works cooperatively with a PXRE located within the proximal promoter [28,29]. Basal and inducible expression of CYP3A4 gene is also regulated by the orphan NR, hepatocyte nuclear factor (HNF4)α [30]. NRs activate their target genes by recruiting or exchanging coactivators with the corepressor complex to the chromatins [31-32]. Chromatin remodeling enzymes catalyze histone modification to allow the binding of transcription factors.

CYP3A4 regulation is also modulated by a broad variety of kinases which phosphorylate the regulatory NRs or their associated proteins. For example, casein kinase (CK) 2-dependent phosphorylation of the heat shock protein 90β (Hsp90β; which binds to and retains PXR in the cytoplasm) was required for induction of a PXR target gene, multi-drug resistance (MDR)1 by the prototypical human PXR (hPXR) ligand, Rifampicin (RIF) [33-35]. Furthermore, the mitogen-activated protein kinase (MAPK), c-JUN N-terminal kinase (JNK) was required for CYP3A4 induction by the vitamin D receptor (VDR) ligand, 1,25-Dihydroxyvitamin D(3) (1,25(OH)(2)D(3)) [36].

Interestingly, phosphorylation was shown to interfere with PXR's subcellular localization, dimerization, DNA binding, and co-regulator interactions, leading to inhibition of its transcriptional activity [33-35]. Kinases such as cyclic-AMP dependent protein kinase A (PKA), PKC,

cyclin dependent kinases, p70 S6K (70-kDa form of S6 kinase), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), serine/threonine kinase DYRK2 can phosphorylate PXR, leading to CYP3A4 inhibition [33-35]. PXR also undergoes additional post-translational modification (PTM)s including ubiquitination, acetylation and SUMOylation, which can impact gene induction by PXR [33-35]. Crosstalk between these PTMs has been reported to affect function of the transcriptional regulators, NF-κB and p53, and it was shown that phosphorylation at Ser 350 affected PXR acetylation [33-35]. Thus, protein phosphorylation may impact multiple PTMs in one or more proteins, and this complex regulatory mechanism may be responsible for CYP3A4 induction by PXR.

Regulation of CYP3A4 enzyme by microRNAs (miRNAs). Post-transcriptional or transcriptional changes in CYP3A4 may be mediated by miRNAs directly targeting the 3'-untranslated region (3'UTR) of CYP3A4 mRNA and indirectly targeting the 3'UTR of NR mRNAs, respectively [37-39]. The involvement of miRNAs in the regulation of CYP enzymes and NRs indicates potential role of miRNAs in the integrated response of cells to drugs and toxins. miRNAs are 19 to 25-nucleotide RNAs that bind to complementary sequences in the 3′-UTR of mRNAs. This recruits a RNA-induced silencing complex to mRNAs to repress protein translation, cleave targeted messages, and degrade mRNAs [37-39]. The broadly conserved miR-27b has been shown to target the 3′UTR of CYP3A4 *in vitro* [38].

Thus, induction or down-regulation of CYP3A4 enzyme can alter the metabolism and clearance of one or more medications in individual patients. These patients will be at a higher risk of undesirable effects of medications. Thus, alteration of CYP3A4-mediated drug metabolism should be a major consideration in developing/implementing treatment regimens for individual patients.

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