



Stress as a Potential Regulatory Factor in the Outcome of Pharmacotherapy

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INTRODUCTION

Accumulating clinical evidence suggests significant inter-individual variations in the efficacy of standard treatment protocols followed for several diseases, such as diabetes, hypertension, depression, cancer and epilepsy, as well as variations in drug-related side effects and toxicity (Zhou et al., 2009; Konstandi et al., 2014; Thummel and Lin, 2014). The problem often becomes more pronounced when multi-drug therapeutic schemes are followed (Konstandi, 2013; Konstandi et al., 2014; Thummel and Lin, 2014; Roughead, 2015). The reasons of this diversity appear to be related to the multi-factorial regulation of the machinery controlling the fate and biological activity of drugs in the body. Cell-signaling, metabolic and transport systems, which are encoded by their respective genes, participate in this machinery and in turn, are regulated by various factors including age, gender, race, lipidemic and endocrinological state (Ingelman-Sundberg, 2004a; Pelkonen et al., 2008; Waxman and Holloway, 2009). The functional integrity of the respiratory, immune, cardiovascular, gastrointestinal, endocrinological and central nervous systems also hold crucial modulatory roles in the machinery controlling drug activity (Ingelman-Sundberg, 2004b; Konstandi, 2013; Konstandi et al., 2014). External modifying factors such as stress stimuli, diet, environmental chemicals, toxicants and drugs, as well as infectious diseases can also modify the outcome and toxicity of pharmacotherapy by influencing the pharmacokinetic and pharmacodynamic profile of drugs (Zhou et al., 2009; Konstandi et al., 2014; Thummel and Lin, 2014; Roughead, 2015). This is attributed to the fact that they can affect the absorption, distribution, metabolism, elimination and activity of drugs (Zhou et al., 2009; Konstandi, 2013; Konstandi et al., 2013, 2014, 2020). In this context, stress plays a central role in the multi-factorial regulation of drugs in the body and in determining a drug's pharmacokinetic profile, as it regulates various enzymes that catalyze the metabolism of the majority of prescribed drugs (Konstandi et al., 2000, 2004, 2005, 2008, 2014; Daskalopoulos et al., 2012; Konstandi, 2013).

DRUG METABOLISM

When a drug enters the body, it is recognized as a potential threat to homeostasis and the detoxifying mechanisms are activated (Handschin and Meyer, 2003; Konstandi et al., 2014), aimed at its metabolic conversion to usually inactive, water soluble metabolites, which can be readily excreted via urine or bile. The liver serves as the major site of drug metabolism, where enzymatic reactions catalyze the metabolic biotransformation of a drug typically in two phases: In Phase I, drugs are metabolized through various oxidation reactions to metabolites with increased water solubility. In Phase II, these metabolic products are conjugated with endogenous molecules, such as glucuronic acid, glutathione or sulfate groups, to form complexes with high water solubility (Gonzalez, 2005). The main families of enzymes that are involved in the metabolism of drugs during Phase I include cytochrome P450s (CYPs), flavin-containing monooxygenases (FMO) and epoxide hydrolases (EH). Enzymes of Phase II include glutathione S-transferases (GST),

UDP-glucuronosyltransferases (UGT), *N*-acetyltransferases (NAT) and sulfotransferases (SULT) (Gonzalez, 2005). Depending on the structure of the drug, one or more of these enzymes catalyze its metabolism leading to modification of the drug's pharmacokinetic, pharmacodynamic and potentially toxicity profiles.

In several cases these enzymatic reactions can result in the formation of biologically active or toxic metabolites that can induce oxidative stress, cell death, carcinogenicity, teratogenesis or other toxic manifestations (Gonzalez and Gelboin, 1994; Guengerich, 2003; Ingelman-Sundberg, 2004a; Cribb et al., 2005; Gonzalez, 2005; Gonzalez and Yu, 2006).

Utilizing the metabolic activation, numerous pro-drugs have been developed over the past few decades, aiming at increased levels of biologically active molecules in the target tissues and less generalized toxic manifestations. Accordingly, pro-drugs are converted into pharmacologically active forms through metabolic activation that is mainly catalyzed by cytochromes (Chen et al., 2004; Gonzalez, 2005). This category of clinically important drugs include levodopa, talampicillin, cyclophosphamide, ftorafur, diazepam, prednisone, protonsil and enalapril, which are converted to dopamine, ampicillin, phosphoramidate mustard, fluorouracil, oxazepam, prednisolone, sulfanilamide and enalaprilat, respectively (Sjovall et al., 1981; Chen et al., 2004; Rooseboom et al., 2004; Sozio et al., 2012; Konstandi, 2013).

CYP-Dependent Drug Metabolism

Cytochrome (CYP) P450s are heme-containing proteins that are widely considered as the most important drug-metabolizing enzymes in humans and other animal species. They are able to collectively recognize and metabolize most structures, due to their broad and overlapping substrate specificities and are expressed virtually in all tissues, with generally highest concentrations and capacity in the liver for the main CYP isozymes. The main CYP isozymes catalyzing the metabolism of the majority of drugs presently in the market and other xenobiotics are arranged into three gene families (CYP1, CYP2, and CYP3) based on their amino acid sequence homology (Nebert, 2000; Nebert and Russell, 2002; Gonzalez, 2005). The most important human CYP isoforms are CYP1A1/2, CYP2A6, CYP2C8/9/19, CYP2D6, CYP2E1, and CYP3A4 (Wormhoudt et al., 1999; Lin et al., 2001; Nebert and Russell, 2002) that catalyze diverse oxidation reactions, including hydroxylations, heteroatom oxidations, heteroatom dealkylations, epoxidations, oxidative group transfer, cleavage of esters, and dehydrogenations (Hollenberg, 1992; Guengerich, 2008). They are also involved in the biosynthesis or catabolism of steroid hormones, neurotransmitters, bile acids, fat-soluble vitamins, fatty acids, and eicosanoids (Spatzenegger and Jaeger, 1995; Guengerich, 2003).

Inter-individual and inter-ethnic variability in drug response and adverse reactions, has been attributed in part, to the polymorphism of CYP genes, including CYP1A1, CYP2A6, CYP2A13, CYP2C8, CYP2D6, CYP3A4, and CYP3A5 (Gonzalez, 2005), and to variations in the distribution of the common

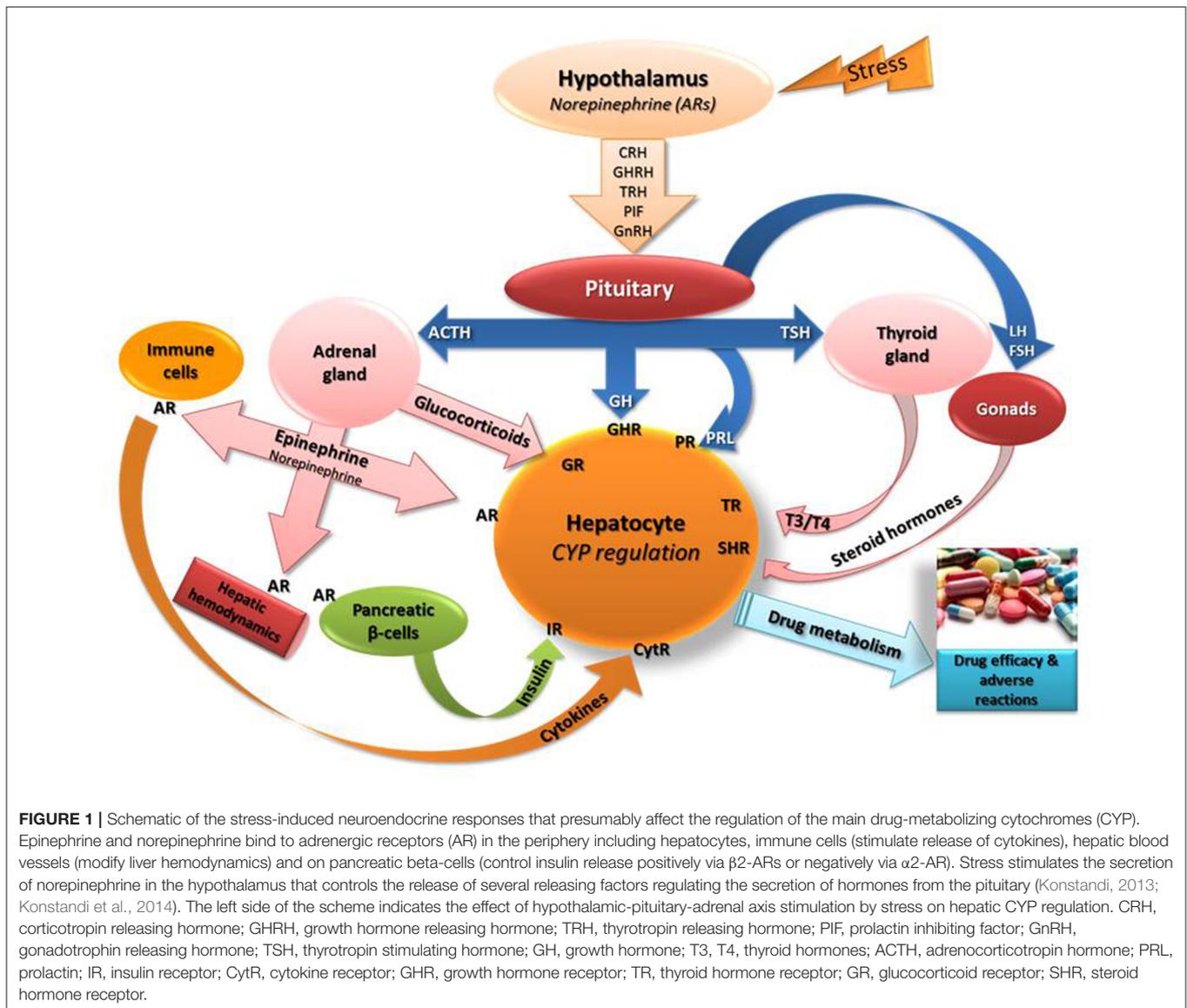
allelic variants of CYP genes among different ethnic populations (Ingelman-Sundberg et al., 2007).

STRESS IMPACT ON CYP-DEPENDENT DRUG METABOLISM

The majority of the CYP genes are inducible and regulated by several external and internal factors, which, as a result, may also influence the fate and effects of drugs through modified enzymatic activity. Some of the emerging factors with increasing clinical significance, as demonstrated by various research groups, are psychophysiological stress and stress-related disorders, which appear to have a major impact on the expression and activity of several CYPs that catalyze the metabolism of widely prescribed drugs (Daskalopoulos et al., 2012; Konstandi, 2013; Konstandi et al., 2014). Our studies indicated that stress can affect constitutive and induced expression levels of CYP isoforms in ways that may critically modify the pharmacokinetic profile of drug-substrates (Konstandi, 2013; Konstandi et al., 2014) (<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>). In particular, preclinical studies employing either early in life maternal deprivation stress, a neurodevelopmental model of stress, which is associated with various psychopathological states during adulthood (Rentesi et al., 2010, 2013) or repeated restraint stress, modified the hepatic drug-metabolizing profile of the animals in a stress-specific manner (Daskalopoulos et al., 2012). The stress-mediated regulation of CYP genes is a complex process involving several mechanisms, including transcriptional regulation through ligand-activated nuclear receptors, such as CAR, PXR and AhR (Nebert and Gonzalez, 1987; Gonzalez, 2005; Daskalopoulos et al., 2012; Konstandi, 2013; Konstandi et al., 2014). It also appears that stress activates major hepatic signal transduction pathways involved in CYP regulation, whereas long-term disturbances of these pathways can promote the accumulation of free radicals and other toxic metabolites in the body with potentially detrimental effects on health (Gonzalez, 2005; Konstandi et al., 2014).

The majority of studies focus on the impact of stress on the CYP-dependent drug metabolism during Phase I. It should be noted though, that stress could affect drug metabolism during Phase II, as it markedly reduces the glutathione content in tissues, when the body is exposed simultaneously to stress and in various toxic factors (Konstandi et al., 1998). This is a condition favoring the development of toxic manifestations, which usually lead to increased morbidity (Konstandi et al., 2014).

It is well documented that exposure to stress triggers various biological events in the body including primarily, activation of hypothalamo-pituitary-adrenal (HPA) axis followed by release of glucocorticoids and epinephrine from adrenal glands (Chrousos and Gold, 1992; Johnson et al., 1992; Chrousos, 2009; Chrousos and Kino, 2009; **Figure 1**). In the stress-induced cascade of events, oxidative stress, increased release of cytokines/NF- κ and modifications in the secretion profiles of hormones, such as growth hormone, thyroid hormones and insulin (Dvorak and



Pavek, 2010) hold critical roles in CYP regulation (Waxman et al., 1991; Woodcroft et al., 2002; Waxman and Holloway, 2009; Konstandi, 2013; Konstandi et al., 2014; **Figure 1**).

Although several studies clearly indicated that stress disrupts normal hepatic drug metabolism (Konstandi et al., 1998, 2000, 2004, 2005, 2014; Daskalopoulos et al., 2012; Konstandi, 2013) it is important to note that stress functioning as a modifying factor of drug metabolism is unique, with properties disparate to those of drugs, which usually have dose- and time-dependent specificities (Daskalopoulos et al., 2012; Konstandi, 2013; Konstandi et al., 2014). Usually, stress up-regulates the constitutive expression of most CYP enzymes, with the exception of *CYP2E1* and *CYP2B*, which are down-regulated. The stress-induced repression of these isozymes could decrease the metabolism of their drugs-substrates, thus resulting in elevated plasma levels of these drugs and consequently,

increased possibility of toxic manifestations (Lang et al., 2001; Arinc et al., 2005; Gonzalez, 2005). On the other hand, it should be noted that psychophysiological stress up-regulates several CYP isozymes belonging to CYP1A, CYP2A, CYP2C, CYP2D, and CYP3A subfamilies that metabolize over 70% of the drugs in the market (Guengerich, 2008; Rendic and Guengerich, 2010; Konstandi, 2013; Konstandi et al., 2014). This induction could result in increased metabolism of their drugs-substrates, and consequently, in reduction of their efficacy. Of particular significance is the fact that stress upregulates CYP2D, which alternatively catalyzes the synthesis of neurosteroids and neurotransmitters, such as dopamine and serotonin, in the brain (Anna Haduch et al., 2013) and the hepatic and brain metabolism of the majority of antidepressant, antipsychotic, antiepileptic and anxiolytic drugs (Niwa et al., 2008; Rendic and Guengerich, 2010; Wang et al., 2014). *CYP2D* expression

is also modified by these drugs and their effects are brain structure-dependent (Anna Haduch et al., 2013). The role of CYP2D in the pathophysiology of neurodegenerative disorders, such as Parkinson's disease, is currently under investigation (Tsuneoka et al., 1998; Mann et al., 2012; Ur Rasheed et al., 2017). From a clinical perspective, the impact of stress on CYP-catalyzed pro-drug metabolism is also very important. The stress-induced up-regulation of CYPs will result in increased pro-drug activation, whereas the CYP repression will result in reduced pro-drug activation, with respective consequences in drug efficacy (Konstandi, 2013; Konstandi et al., 2014).

The assessment of the effect of stress on drug metabolism, should not overlook the fact that chronic uncontrolled stress is considered as a causative factor in the pathogenesis of several disease states including cancer, depression, inflammatory diseases and those of metabolic syndrome, such as diabetes mellitus, obesity and hypertension (Gold et al., 1988; McEwen, 2000; Kloet et al., 2005). Patients suffering from these diseases have modified hormonal, immune and nutritional profiles compared to normal population (Chrousos and Gold, 1992; Tsigos and Chrousos, 2002), condition that could decisively affect their hepatic drug-metabolizing capacity (Konstandi, 2013; Konstandi et al., 2014). However, it remains to be determined whether the disease-related alterations in drug metabolism can be attributed to the disease itself, or they are associated with deregulation of the stress response system, which usually underlies the pathophysiology of the afore-mentioned diseases.

It is well established that the major effectors of the stress response, glucocorticoids and epinephrine, play primary, and partly distinct roles in the stress-induced regulation of CYPs by employing distinctive signaling pathways. Accordingly, drugs with sympathomimetic properties, or those acting as adrenergic receptor-blockers, or modifying the glucocorticoid, growth hormone, thyroid and insulin status, may influence the CYP-catalyzed drug metabolism, and therefore, the pharmacokinetics and pharmacodynamics of co-administered drugs and xenobiotics (Konstandi, 2013; Konstandi et al., 2014). The available evidence suggests that clinically applied drug dosing-regimes should be designed by taking into account possible drug-stress, drug-glucocorticoid and drug-adrenergic receptor interactions, which are known to modify drug efficacy and toxicity. Moreover, in addition to the pharmacologic profile of a drug, clinicians may consider the stress profile of the

patient when determining the optimal dosing regime to ensure the highest possible drug efficacy and the minimum adverse reactions (Konstandi, 2013; Konstandi et al., 2014).

DISCUSSION

Increasing evidence suggests that psychophysiological stress plays a critical role in modifying the pharmacological and toxicological potency of many clinically used drugs by affecting the activity of CYP isozymes that catalyze their metabolism. Stress can affect the CYP-catalyzed drug metabolism in an enzyme- and stress-specific manner thus modifying the pharmacokinetic and pharmacodynamic profile of a drug and subsequently, the outcomes of drug therapy and toxicity. It is well documented that AR-linked pathways and glucocorticoids play major and partly, distinct roles in the stress-mediated regulation of CYPs. Although the mechanistic data have been obtained largely from preclinical studies, they provide solid evidence for the potential consequences of psychophysiological stress on drug metabolism in humans. This hypothesis is based primarily on the high similarity of the stress system functioning between mammals. It is therefore suggested that when designing a therapeutic scheme, particularly when it is based on multiple drugs, or on drugs with small therapeutic windows or with significant adverse effects, the patient's stress profile should be considered. In order to optimize the therapeutic efficacy of the drugs included in the prescribed scheme and minimize their side effects, elimination of stress is a prerequisite. Furthermore, when the treatment regimen includes drugs that affect the AR-linked pathways or the stress-related hormonal signaling, the drug dosing algorithms potentially need to be adjusted accordingly. Finally, the studies indicating the multi-faced and multi-level interplay between drug and stress system response, underscore the need of pharmacogenetic testing in the implementation of personalized medicine (Rostami-Hodjegan and Tucker, 2007; Zanger and Schwab, 2013).

AUTHOR CONTRIBUTIONS

MK drafted the original manuscript. EJ and ML critically revised the manuscript. All authors agree for the content of the work and approved it for publication.

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Conflict of Interest: ML was employed by Neomind Tech.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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