COMMENTARY

Stress as a potential regulator of pharmacotherapy outcomes

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ABSTRACT

Accumulating clinical evidence suggests that there are significant inter-individual differences in the efficacy of standard treatment protocols used for a variety of diseases, including diabetes, hypertension, depression, cancer, and epilepsy, as well as differences in drug-related side effects and toxicity. When multi-drug therapy regimens are used, the issue frequently becomes more apparent. The causes for this variation appear to be connected to the multi-factorial regulation of the machinery governing drug destiny and biological activity in the body. This machinery includes cell-signaling, metabolic, and transport systems, which are encoded by their respective genes and, in turn, are controlled by a variety of parameters such as age, gender, race, lipidemic, and endocrinological status. The respiratory, immunological, cardiovascular, gastrointestinal, endocrinological, and central neurological systems all play important modulatory roles in the machinery that regulates drug action. External modifying variables such as stress, nutrition, ambient chemicals, toxicants, and medications, as well as infectious disorders, can all influence the result and toxicity of pharmacotherapy by changing the chemicals, toxicants, and medications, as well as infectious disorders, can all influence the result and toxicity of pharmacotherapy by changing the pharmacokinetic and pharmacodynamics profiles of pharmaceuticals. This is due to the fact that they can interfere with medication absorption, distribution, metabolism, excretion, and action. In this regard, stress is important in the multifactorial control of medications in the body and in shaping a drug's pharmacokinetic profile since it affects many enzymes that catalyze the metabolism of the majority of prescription pharmaceuticals.

Key Words: *Hypertension*

INTRODUCTION

When a drug enters the body, it is recognized as a possible danger to homeostasis, and detoxification mechanisms are engaged, with the goal of metabolic conversion to typically inactive, water soluble metabolites that may be eliminated easily via urine or bile. The liver is the primary location of drug metabolism, where enzyme processes accelerate a drug's metabolic biotransformation in two stages: During Phase I, medicines are converted to metabolites with higher water solubility via different oxidation processes. In Phase II, these metabolic products are conjugated with endogenous molecules such as glucuronic acid, glutathione, or sulphate groups to produce water-soluble complexes.

Cytochrome P450s (CYPs), Flavin-Containing Monoxygenases (FMO), and epoxide hydrolases are the primary groups of enzymes involved in drug metabolism during Phase I. Glutathione S-Transferases (GST), UDP-Glucuronosyl Transferases (UGT), N-Acetyl Transferases (NAT), and sulfotransferases are examples of Phase II enzymes. Depending on the drug's structure, one or more of these enzymes catalyze its metabolism, altering the drug's pharmacokinetic, pharmacodynamics, and potentially toxicity profiles. In some situations, these enzymatic processes can produce physiologically active or toxic metabolites, which can cause oxidative stress, cell

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death, carcinogenesis, teratogenesis, or other toxic symptoms. Numerous pro-drugs have been produced during the last several decades that use metabolic activation to achieve higher amounts of physiologically active molecules in target tissues and fewer broad adverse symptoms. Pro-drugs are therefore transformed into pharmacologically active forms by metabolic activation, which is mostly mediated by cytochromes. Levodopa, talampicillin, cyclophosphamide, ftorafur, diazepam, prednisone, protonsil, and enalapril are therapeutically essential medications that are transformed to dopamine, ampicillin, phosphoramide mustard, fluorouracil, oxazepam, prednisolone, sulfanilamide, and enalaprilat, respectively.

Cytochrome P450s are heme-containing proteins usually regarded as the most significant drug-metabolizing enzymes in humans and other animal species. Because of their wide and overlapping substrate specificities, they can collectively identify and metabolize most structures and are expressed in practically all tissues, with the primary CYP isozymes having the highest concentrations and capability in the liver. Based on amino acid sequence homology, the principal CYP isozymes accelerating the metabolism of the majority of medicines currently on the market and other xenobiotics are classified into three gene families (CYP1, CYP2, and CYP3). The most important human CYP isoforms are CYP1A1/2, CYP2A6, CYP2C8/9/19, CYP2D6, CYP2E1, and CYP3A4, which catalyze a wide range of oxidation reactions such as hydroxylation's, heteroatom oxidations, heteroatom dealkylations, epoxidations, oxidative group transfer, ester cleavage, and dehydrogenations. They also participate in the production or catabolism of steroid hormones, neurotransmitters, bile acids, fat-soluble vitamins, fatty acids, and eicosanoids.

The majority of CYP genes are inducible and controlled by a variety of external and internal stimuli, which may impact drug destiny and effects via altered enzyme activity. 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 commonly prescribed drugs, are among the emerging factors with increasing clinical significance, as demonstrated by various research groups. Our findings suggest that stress can alter the constitutive and induced expression levels of CYP isoforms, potentially altering the pharmacokinetic profile of drug-substrates.

Preclinical studies, in particular, using either early in life maternal deprivation stress, a neurodevelopmental model of stress associated with various psychopathological states during adulthood, or repeated restraint stress, altered the animals' hepatic drug-metabolizing profile in a stress-specific manner. Stress-mediated CYP gene regulation is a complicated process involving several mechanisms, including transcriptional control via ligand-activated nuclear receptors such as CAR, PXR, and AhR. Stress also appears to stimulate main hepatic signal transduction pathways involved in CYP control, whereas long-term disruptions of these pathways can promote the buildup of free radicals and other harmful compounds in the body, potentially causing health problems.

During Phase I, the bulk of research focus on the effect of stress on CYP-dependent drug metabolism. It should be emphasized, however, that stress may have an impact on medication metabolism during Phase II since it significantly lowers glutathione levels in tissues when the body is subjected to stress and numerous harmful substances at the same time. This is a state that promotes the emergence of toxic symptoms, which generally result in increased morbidity.

It is generally established that stress causes a variety of biological reactions in the body, the most prominent of which is the activation of the Hypothalamo-Pituitary-Adrenal (HPA) axis, followed by the release of glucocorticoids and epinephrine from the adrenal glands. In the stress-induced cascade of events, oxidative stress, increased cytokine/NF-k release, and changes in hormone secretion patterns, such as growth hormone, thyroid hormones, and insulin, play essential roles in CYP regulation.

The assessment of the effect of stress on drug metabolism should not overlook the fact that chronic uncontrolled stress is thought to be a causative factor in the pathogenesis of several disease states, including cancer, depression, inflammatory diseases, and metabolic syndrome diseases like diabetes mellitus, obesity, and hypertension. Patients with these disorders have altered hormonal, immunological, and nutritional profiles as compared to the general population, which may have a significant impact on their hepatic drug-metabolizing ability. However, it is unclear whether the illness-related changes in drug metabolism may be attributable to the disease itself or to dysregulation of the stress response system, which often underpins the pathophysiology of the aforementioned disorders.

Although several studies have clearly shown that stress disrupts normal hepatic drug metabolism, it is important to note that stress's role as a modifying factor of drug metabolism is distinct, with properties that differ from those of drugs, which typically have dose- and time-dependent specificities. Most CYP enzymes are up-regulated in response to stress, with the exception of CYP2E1 and CYP2B, which are down-regulated. Stress-induced suppression of these isozymes may reduce the metabolism of their drug-substrates, resulting in raised plasma levels of these medications and, as a result, an increased risk of toxic symptoms.

It is widely known that the principal stress effectors, glucocorticoids and epinephrine, play key and partially different roles in the stress-induced regulation of CYPs *via* unique signaling pathways. As a result, drugs with sympathomimetic properties, or those that act as adrenergic receptor blockers, or those that alter the glucocorticoid, growth hormone, thyroid, and insulin status, may influence CYP-catalyzed drug metabolism and, as a result, the pharmacokinetics and pharmacodynamics of co-administered drugs and xenobiotics.

According to the data, therapeutically applicable medication dosage regimens should be planned to account for potential drug-stress, drug-glucocorticoid, and drug-adrenergic receptor interactions, which are known to alter drug effectiveness and toxicity. Furthermore, in addition to a medicine's pharmacologic profile, doctors may consider the patient's stress profile when choosing the best dosage regime to achieve the maximum potential pharmacological effectiveness with the fewest adverse responses.

Increasing data demonstrates that psychophysiological stress modifies the pharmacological and toxicological efficacy of many therapeutically used medications by influencing the activity of the CYP isozymes that catalyze their metabolism. Stress can influence the pharmacokinetic and pharmacodynamics profile of a medication, as well as the results of pharmacological therapy and toxicity, by affecting CYP-catalyzed drug metabolism in an enzyme- and stress-specific way. It is widely established that AR-linked pathways and glucocorticoids play significant and, to some extent, separate roles in the stress-mediated regulation of CYPs. Although the mechanistic data are primarily from

preclinical research, they give strong evidence for the potential effects of psychophysiological stress on medication metabolism in people. This notion is mostly based on the significant degree of similarity in how animals' stress systems work. It is consequently recommended that the patient's stress profile be addressed when establishing a therapy scheme, particularly when it is based on several medications, drugs with narrow therapeutic windows, or drugs with substantial adverse effects. The reduction of stress is a necessity for optimizing the therapeutic efficacy of the pharmaceuticals contained in the prescribed scheme and minimizing their negative effects. Furthermore, when medications that alter AR-linked pathways or stress-related hormonal signaling are included in the treatment regimen, the drug dosage algorithms may need to be changed correspondingly.