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Review

Consequences of psychophysiological stress on cytochrome P450-catalyzed drug metabolism

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ABSTRACT

Most drugs are metabolized in the liver by cytochromes P450 (CYPs). Stress can modify CYP-catalyzed drug metabolism and subsequently, the pharmacokinetic profile of a drug. Current evidence demonstrates a gene-, stress- and species-specific interference in stress-mediated regulation of genes encoding the major drug-metabolizing CYP isozymes. Stress-induced up-regulation of CYPs that metabolize the majority of prescribed drugs can result in their increased metabolism and consequently, in failure of pharmacotherapy. In contrast, stress-induced down-regulation of CYP isozymes, including *CYP2E1* and *CYP2B1/2*, potentially reduces metabolism of several toxicants and specific drugs-substrates resulting in increased levels and altered toxicity. The primary stress effectors, the adrenergic receptor-linked pathways and glucocorticoids, play primary and distinct roles in stress-mediated regulation of CYPs. Evidence demonstrates that stress regulates major drug metabolizing CYP isozymes, suggesting that stress should be considered to ensure pharmacotherapy efficacy and minimize drug toxicity. A detailed understanding of the molecular events underlying the stress-dependent regulation of drug metabolizing CYPs is crucial both for the design of new drugs and for physiology-based pharmacokinetic and pharmacodynamic modeling.

Contents

1. Introduction

Stress is a constant factor in modern life and has become one of the most significant health problems in modern societies. The organism's response to stress is a complex, multifactorial process that involves an elaborate neuroendocrine, cellular and molecular infrastructure. While it is well established that repeated or chronic stress can have deleterious effects on the health and well-being of individuals, the molecular mechanisms linking stress to disease initiation and progression are not fully understood. As such,

Abbreviations: CYP, Cytochrome P450; PAH, polycyclic aromatic hydrocarbon; EROD, ethoxyresorufin 7-dealkylase; PROD, pentoxyresorufin 7-dealkylase; B[α]P, benzo[α]pyrene; PNP, *p*-nitrophenol hydroxylation; FMO, flavin-containing monoxygenases; EH, epoxide hydrolases; GST, glutathione S-transferases; UGT, UDP-glucuronosyltransferase; NAT, *N*-acetyltransferases; SULT, sulfotransferases; CES, carboxylesterase; Ahr, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; CRH, corticotropin-releasing hormone; LC, locus ceruleus; NE, norepinephrine; HPA, hypothalamo-pituitary adrenal axis; PVN, paraventricular nucleus; ARs, adrenergic receptors; beta-NF, beta-naphthoflavone.

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investigations are currently focusing on dissecting the biological pathways linking stress and health.

Physiological response to stress is essentially mediated by the hypothalamic–pituitary–adrenal (HPA) axis and the central and peripheral components of the autonomic nervous system. The integrity and precision of their interactions with other components of the central nervous system are essential for mounting a successful stress response. Chronic stress caused by exposure to persistent or frequently repeated stressors induces a prolonged activation of the stress response systems. The deleteriously overloaded system is faced with complications due to prolongation of the adaptive response. In addition to the exquisitely orchestrated adaptive response that challenges the homeostasis of the organisms, stress also challenges the homeostasis and integrity of the cell. A complex intra-cellular signaling network enables cells to sense environmental changes and to adjust the cellular processes including the bioenergetic, thermogenic and oxidative responses accordingly, in order to re-establish homeostasis. For example, chronic psychological stress is not only associated with a greater risk for depression, but contributes to chronic diseases, such as heart disease, obesity and infectious diseases (Chrousos and Gold, 1992; Chrousos and Kino, 2009; Johnson et al., 1992; Tsigos and Chrousos, 2002).

Drug metabolism is one of the major factors contributing to pharmacokinetics, in addition to absorption, distribution and elimination. The major site of drug metabolism is the liver, and in healthy individuals the metabolic processes are in homeostasis. Drug metabolizing enzymes include both phase I, comprised mainly of cytochromes P450 (CYPs) that catalyze oxidation reactions, and phase II enzymes that catalyze conjugation reactions. Modification of the hepatic signaling pathways will affect drug metabolism and long-term disturbance of the metabolic pathways can lead to intracellular accumulation of free radicals and other metabolic products that are potentially toxic (Naik et al., 2013). It is well known that the expression of *CYPs*[1] can be altered by various diseases, including diabetes, obesity, depression, infections and inflammation, all of which have been associated with chronic stress (Arinc et al., 2005; Johnson et al., 1992; Konstandi et al., 2004; Kotsovolou et al., 2010).

Stress can change the pharmacokinetic profile of a drug in multiple ways. For example, stress can influence gastrointestinal function and absorption, lipid distribution and blood flow, all known to be relevant to pharmacokinetics (Mangoni and Jackson, 2004). Stress can also increase the free fatty acid contents due to glucocorticoid-induced fat mobilization, which in turn, may displace drugs from albumin binding sites. In the circulatory system, serum albumin is an important carrier agent for both, free fatty acids and drugs, such as the antidiabetic sulfonylureas (i.e., acetohexamide, tolbutamide and gliclazide), which compete for the same binding sites on serum albumin (Anguizola et al., 2013). The reduced plasma protein drug-binding capacity can have serious consequences for pharmacokinetics, potentially resulting in sub-therapeutic or toxic levels of numerous drugs, such as oral anti-coagulants, beta-lactames, beta-blockers and calcium channel-blockers, among others (Pervanidou and Chrousos, 2012). In addition to these systemic effects, studies have shown that stress may alter the activity of the major drug-metabolizing enzymes in the liver, particularly the CYPs. The clinical significance of understanding the biological pathways linking stress to the regulation of cytochromes has spurred research in dissecting the differential roles of the two primary effectors of the stress response system, namely glucocorticoids and adrenergic pathways, on several signaling pathways regulating the expression of various CYP genes.

This review summarizes the recent progress in our understanding on how stress activated signaling pathways can influence hepatic drug metabolism. Emphasis is given on the role of glucocorticoid- and adrenergic receptor-linked pathways in the regulation of CYPs. In our view, this information is crucial for a rational assessment of stress–drug interactions and for developing improved drug dosing algorithms for effective and safe pharmacotherapy.

2. The stress response system

Stress has been defined as a state of threatened homeostasis caused by intrinsic or extrinsic adverse forces. This challenge to homeostasis is counteracted by a complex repertoire of physiologic and behavioral responses that aim to reestablish the threatened equilibrium of the organism. Although details of the pathways by which the brain translates stressful stimuli into an integrated biological response are incompletely understood, it is well-accepted that deregulation of these responses to stress can have severe consequences, and have been linked to the pathophysiology of various disorders (Chrousos, 2009; Johnson et al., 1992).

Initially, exposure to stress stimulates the primary components of the stress response system located within the central nervous system. The central effectors of the stress system are tightly interconnected and include the hypothalamic hormones

[1] *Note*: In the nomenclature of cytochromes, the human and rat genes are presented with capital letters in italics (e.g. *CYP2E1*). The corresponding murine gene is presented with small letters in italics (e.g. *Cyp2e1)*. Proteins are presented with capital letters (e.g. CYP2E1).

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