

The role of cytochromes P450 in the metabolism of selected antidepressants and anxiolytics under psychological stress

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In today's modern society, it seems to be more and more challenging to cope with life stresses. The effect of psychological stress on emotional and physical health can be devastating, and increased stress is associated with increased rates of heart attack, hypertension, obesity, addiction, anxiety and depression. This review focuses on the possibility of an influence of psychological stress on the metabolism of selected antidepressants (TCAs, SSRIs, SNRIs, SARIs, NDRIs and MMAs) and anxiolytics (benzodiazepines and azapirone), as patients treated with antidepressants and/or anxiolytics can still suffer from psychological stress. Emphasis is placed on the drug metabolism mediated by the enzymes of Phase I, typically cytochromes P450 (CYPs), which are the major enzymes involved in drug metabolism, as the majority of psychoactive substances are metabolized by numerous CYPs (such as CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2A6, CYP2D6, CYP3A4). As the data on the effect of stress on human enzymes are extremely rare, modulation of the efficacy and even regulation of the biotransformation pathways of drugs by psychological stress can be expected to play a significant role, as there is increasing evidence that stress can alter drug metabolism, hence there is a risk of less effective drug metabolism and increased side effects.

Key words: drug metabolism, cytochrome P450, psychological stress, antidepressants, anxiolytics

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INTRODUCTION

The term “mental health” can be defined as the absence of mental disease or, respectively, it is a state of being that includes the biological, psychological and social factors which contribute to the mental state. The World Health Organization (WHO) also includes the ability to realize potential and the ability to cope with normal life stresses as a significant component of mental health¹.

In fact, in today's modern society, it seems to be more and more challenging to successfully cope with life stresses, as stress has been dubbed the “Health Epidemic of the 21st Century” by the WHO. Increased level of stress is associated with increased rates of heart attack, hypertension, obesity, addiction, anxiety, depression and other disorders².

The diagnosis and treatment of mental health are as old as civilization, although the treatment of mental disorders included numerous extreme approaches. Leucotomy, insulin shock therapy and induced epileptic seizures became a standard treatment in the first half of the 20th century. However, the development of effective psychiatric medication began in the 1950s and is still in a phase of rapid development³.

There are several commonly used classes of antidepressants. Most of them increase the synaptic availability of monoamine neurotransmitters and neuromodulators such as serotonin, norepinephrine and/or dopamine⁴. Selected classes of antidepressants are also used in the pharmacotherapy of anxiety disorders. In addition,

benzodiazepines are also valuable in the treatment of anxiety⁵.

Being foreign substances to the organism, medications such as antidepressants and anxiolytics, after their absorption and distribution in the body, are metabolized by a variety of chemical reactions involving oxidation, reduction and hydrolysis (catalyzed by Phase I enzymes) and/or glucuronidation, sulfation, acetylation and methylation (catalyzed by Phase II enzymes), which should facilitate their excretion^{6,8}.

In this review, emphasis is placed on the drug metabolism mediated by the enzymes of Phase I, typically cytochromes P450 (CYPs), which are the major enzymes involved in drug metabolism (~75% of marketed drugs) (ref.^{7,8}). The expression and also the functionality of CYPs are influenced by numerous genetic and non-genetic factors⁸. In addition, the activity of CYPs can be influenced by stress⁹.

We focused on selected drug-metabolizing CYP enzymes which significantly participate in metabolizing antidepressants and anxiolytics, as patients treated with antidepressants and/or anxiolytics can still suffer from psychological stress.

STRESS AND MENTAL DISORDERS - ANXIETY AND DEPRESSION

The term stress characterizes the effects of any circumstances (threats) that could disrupt homeostasis¹⁰. All

these circumstances, also called stressors, create psychological stress, which is an adaptation to the fight-or-flight response¹¹. The two major components involved in the response to the stressors are the sympathetic-adreno-medullar (SAM) axis and the hypothalamus-pituitary-adrenal (HPA) axis¹².

Based on the duration of the effect of stressors, we can define stress as acute or chronic. Stressors that elicit acute stress are intense short-term exposures (minutes or hours) and typically have a clear starting and ending point. However, if acute stressors are experienced over a long period of time, they can turn into chronic stressors. In contrast, stressors that elicit chronic stress occur on a time scale of weeks, months, even potentially years¹³. Chronic stress most likely results in long-term or permanent changes in emotional, physiological, and behavioral responses, as the prolonged or repeated activation of the SAM and HPA axis can interfere with their control of other physiological systems. This can result in an increased risk of various disorders¹⁴.

As studies have shown, there is a clear association between stress and anxiety¹⁵. Also, stressful life circumstances can lead to anxiety disorders, and these patients are most likely prone to develop depression¹⁶. In fact, depression along with anxiety are stress-related disorders with similar symptoms¹⁷. Anxiety disorders are a group of disorders characterized by feelings of anxiety and fear accompanied by behavioral disturbances¹⁸. Specific (isolated) phobias, panic disorder, social anxiety disorder and generalized anxiety are among the most common anxiety disorders. The term “depression” refers to major depressive disorder, and it is a mental state characterized by loss of pleasure or interest in almost all activities¹⁷.

TREATMENT OF DEPRESSION AND ANXIETY DISORDERS

The treatment of clinical depression and all the drugs currently available target neurotransmitters – the monoamines (serotonin, norepinephrine and/or dopamine). Commonly used classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and serotonin antagonists and reuptake inhibitors (SARIs). The first generation of antidepressants - tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are still occasionally used¹⁹. Based on the “monoamine theory” of depression, the mechanism of action of these antidepressants is to increase the synaptic availability of the neurotransmitters²⁰. However, this traditional neurobiological hypothesis cannot fully explain the depressive disorders, and does not explain the effects of antidepressants used in the treatment of anxiety disorders²¹. The answer to this inconsistency in the “monoamine theory” can be found in the “hypothesis of neuroplasticity”, where the chronic antidepressants change neuroplasticity, cellular resilience and synaptic plasticity²².

The treatment of various anxiety disorders is aimed at targeting specific brain neurotransmitter systems. Selected drugs of the antidepressant classes such as SSRIs, SNRIs and TCA are used in the pharmacotherapy of various anxiety disorders⁵. Benzodiazepines, a class of psychoactive drugs developed to replace barbiturates, are generally regarded as a proven treatment for acute anxiety disorders. The action of benzodiazepines is based on the effects mediated by the γ -aminobutyric acid (GABA) receptor complex²³, and the treatment often has an immediate onset⁵.

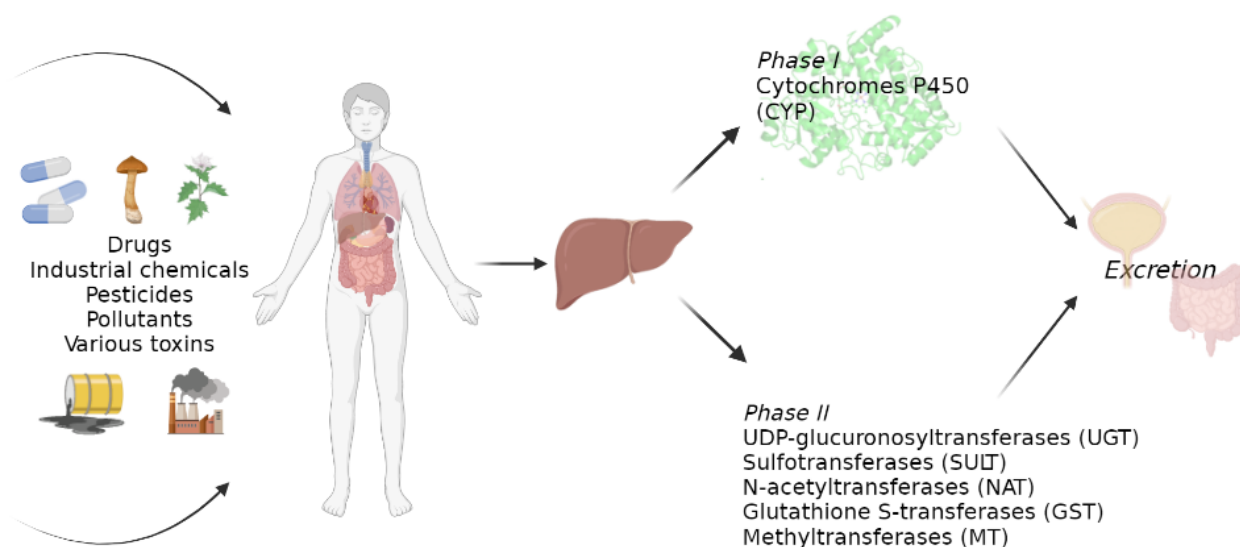


Fig. 1. Biotransformation of xenobiotics in liver. Drugs, industrial chemicals, pesticides, pollutants, secondary plant metabolites and various toxins are metabolized by enzymes (abbreviations in parenthesis) of Phase I and Phase II of xenobiotic metabolism. These metabolic pathways modify the structure of foreign compounds, leading to their eventual excretion from an organism. (Created with BioRender.com)

DRUG METABOLISM

Antidepressants and anxiolytics, being foreign compounds to the organism, are metabolized by the biotransformation enzymes of Phase I and Phase II (ref.²⁴). They play a central role in the biotransformation, detoxification and eventually elimination of exogenous compounds (Fig. 1) (such as drugs, industrial chemicals, pesticides, pollutants, secondary plant metabolites and various toxins) (ref.²⁵). However, xenobiotic biotransformation can also increase/activate the toxicity of a foreign compound; more frequently it decreases the toxicity of a compound.

There are an extensive number of Phase I and Phase II enzymes, and most of them exist in several polymorphic forms⁸. In humans, the main detoxification organ is the liver, although these enzymes can be found in almost all tissues. In addition to the liver, the gastrointestinal tract, lungs, kidneys, brain and other organs may significantly contribute to the biotransformation of drugs²⁶.

The most important enzymes of Phase I of xenobiotic metabolism are cytochromes P450 (CYPs) – a superfamily of microsomal enzymes which mostly catalyze oxidation reactions. CYPs almost always act as monooxygenases (mixed-function oxidases) (ref.²⁷). They are known for their role in drug and xenobiotic biotransformation, however many of them catalyze specific reactions needed for the biotransformation of endogenous compounds such as steroid hormones, prostaglandins,

bile acids and more. In humans, 57 genes encoding CYPs are grouped according to their sequence similarity into 18 families and 44 subfamilies. Among the products of these genes, only enzymes of families CYP1, CYP2 and CYP3 (and to some extent also of CYP4) participate in the metabolism of the majority of drugs⁸.

Enzymes of Phase II (Fig. 1) mainly consist of the transferase enzymes, including UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), N-acetyltransferases (NATs), glutathione S-transferases (GSTs) and methyltransferases (mainly thiopurine S-methyltransferase (TPMT) and catechol O-methyl transferase (COMT) (ref.²⁸). The conjugation reactions catalyzed by Phase II enzymes increase hydrophilicity and improve excretion in the bile and/or the urine. Compounds undergoing the conjugation reactions need to contain a hydroxyl functional group, which can be present in the parent molecule and/or introduced into their structure after reaction with the Phase I enzymes (such as CYPs) (ref.²⁴).

FACTORS INFLUENCING DRUG-METABOLIZING CYTOCHROMES P450

There are numerous intrinsic and extrinsic factors, both genetic and non-genetic, that influence the expression and function of cytochromes P450 (Fig. 2).

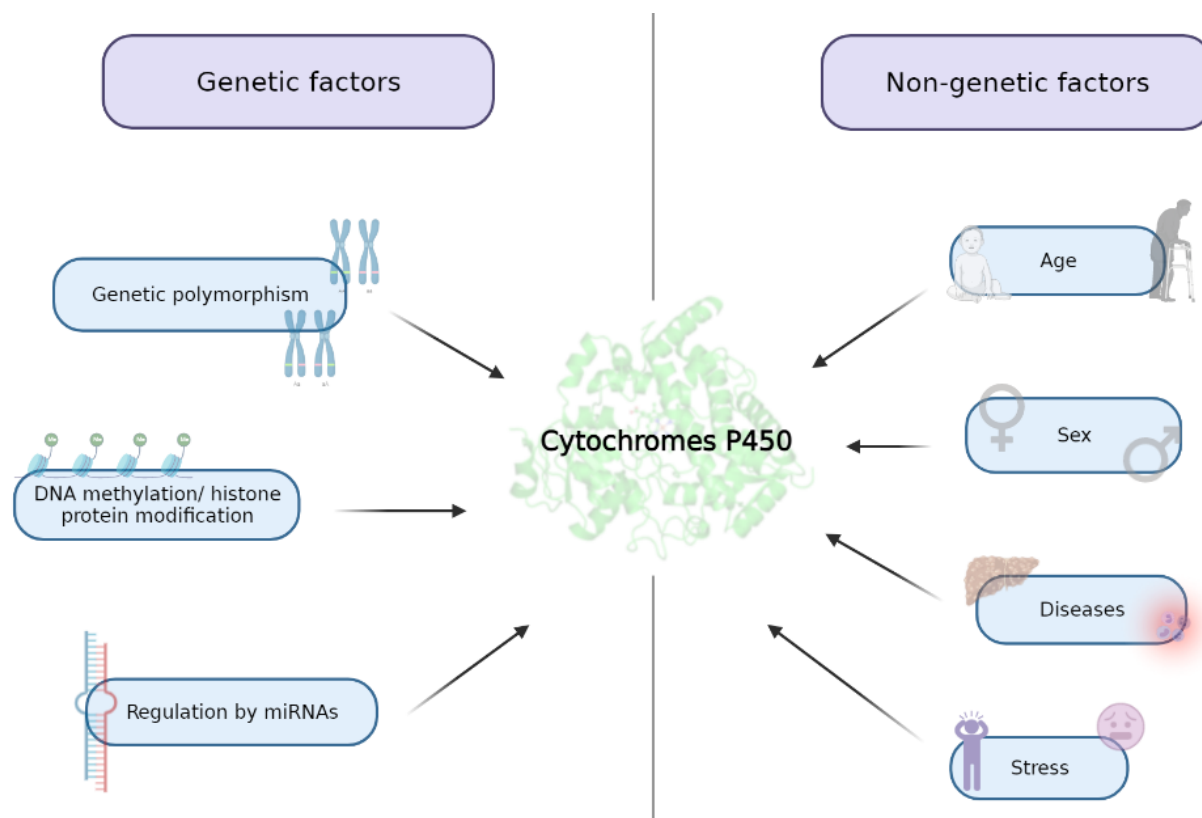


Fig. 2. Factors influencing cytochromes P450. Genetic and non-genetic factors are able to influence the expression and function of various cytochromes P450. Genetic factors include genetic polymorphism and epigenetic processes such as DNA methylation, histone protein modification, and regulation by microRNAs (miRNAs). Non-genetic factors include age, sex, various diseases and also stress. (Created with BioRender.com)

Genetic variations (genetic polymorphisms) determine individual response to drugs, and are often responsible for the diversity in drug responses²⁹. Genetic polymorphism is able to significantly impact drug metabolism, and is an important factor in the prediction of pharmacokinetics and drug response. Other genetic factors that can influence cytochromes P450 are epigenetic processes such as DNA methylation, histone protein modification and the involvement of the microRNAs in regulating the expression of drug-metabolizing genes³⁰.

In addition, non-genetic host factors such as sex, age, various diseases, hormonal influences and other factors play an important role in the regulation and function of drug-metabolizing cytochromes P450. Sex-specific expression has now been reported for CYP enzymes, although the issue of sex-specific expression, mostly for other CYPs, still needs to be clarified³¹. Age is also an important factor for drug metabolism. In neonates, cytochromes P450 are fully developed after the first year of life, and there is a decreased ability to clear drugs in the elderly⁸. The impact of various diseases on drug metabolism is mostly associated with inflammation and infection, and the effects of inflammatory cytokines such as interleukins 1 β and 6 (IL-1 β , and IL-6), tumor necrosis factor alpha (TNF α), and interferons (IFN) α or γ (ref.³²).

This review focuses on another important factor influencing cytochromes P450, as there is increasing evidence that stress can alter drug pharmacokinetics and drug metabolism, hence there is a risk of less effective drug metabolism and increased side effects³³.

CYTOCHROMES P450, STRESS AND METABOLISM OF PSYCHOACTIVE COMPOUNDS

Stress, one of the most significant problems in modern life, is a complex and multifactorial process. The response to stress is mediated by the central nervous system with its main components - the corticotropin-releasing hormone/arginine-vasopressin and locus ceruleus nor-epinephrine/sympathetic neurons of the hypothalamus and brain stem. These components regulate the activity of the hypothalamic-pituitary-adrenal axis (HPA) and the systemic/adreno-medullary sympathetic nervous systems (SNS), and their activation leads to systemic elevations of glucocorticoids and catecholamines maintaining homeostasis³⁴. The stress response involves changes in the nervous, cardiovascular, endocrine and immune systems¹⁶. In addition, stress can change the pharmacokinetic profile of a drug and also its metabolism. Stress can modulate gastrointestinal function, adsorption and blood flow, resulting in changed pharmacokinetics of the drug. It can also influence the binding of the drugs to albumin, due to glucocorticoid-induced fat mobilization causing an increase in the free fatty acid content, which may displace drugs from albumin binding sites.

As was mentioned above, stress can also significantly impact some of the drug-metabolizing systems, mainly enzymes of Phase I - cytochromes P450 (ref.⁹). Various

CYPs, such as CYP3A4, CYP1A1/2, CYP2A6, CYP2B6 and CYP2C9/19, are in fact affected by the glucocorticoids. Catecholamines and the adrenergic-dependent systems have an impact on the regulation of the expression of several CYPs, however the role of these effectors in regulating CYPs is still unclear³⁵. Daskalopoulos and colleagues have demonstrated that epinephrine has a positive effect on CYP3A, CYP2C and CYP2D regulation³⁵. Their study also showed that glucocorticoids upregulated hepatic CYP3A expression. In fact, stress-released glucocorticoids initiate CYP gene transcription, and it is also possible that they can enhance the regulation of CYPs (ref.³³). It is possible that stress can potentially have harmful consequences on the effectiveness and toxicity of a medication, hence a better understanding of the factors that are able to alter the biotransformation of drugs is important. The possible effect of psychological stress on the CYP metabolism of selected antidepressants and anxiolytics is shown in Table 1.

CYP1A2, unlike CYP1A1, is mainly expressed in the liver and contributes to the biotransformation of several environmental pollutants and carcinogens, as well as playing a significant role in the metabolism of several clinically important drugs⁸. CYP1A2 contributes to the biotransformation of duloxetine, clomipramine, and fluvoxamine. The effect of stress on CYP1A2 is not only stress-specific, but also species-specific⁹. In mice, chronic psychosocial stress caused a decrease in the mRNA expression of CYP1A2 and also the activity of CYP1A enzymes¹⁰. In contrast, repeated mild unpredictable stress increased the CYP1A1/2 enzymatic activity in rats⁹. There are also studies showing that acute restraint stress increases CYP1A2 expression in murine livers³⁶.

CYP2A6 is a genetically polymorphic enzyme and is responsible for the biotransformation of nicotine and several drugs³⁷. It partially contributes to the metabolism of vortioxetine. Psychological stress is able to increase the expression and activity of CYP2A5 in the murine liver³³.

CYP2B6, one of the minor drug-metabolizing CYP enzymes in the liver, is one of the most polymorphic CYP genes in humans, and its expression is highly variable³⁸. CYP2B6 catalyzes the biotransformation of sertraline and bupropion, and participates in the metabolism of paroxetine. Exposure to repeated restraint stress can modify CYP2B, as it was proven that the CYP2B1/2-catalyzed penthoxyresorufin 7-dealkylase activity was significantly decreased in the rat liver. Mild unpredictable stress had no effect at all³⁹.

In humans, members of the CYP2C subfamily are responsible for the metabolism of more than 20% of all pharmaceutical drugs, including some of the most frequently prescribed medications, and also a number of endogenous compounds⁴⁰. CYP2C19 is responsible for the metabolism of amitriptyline, imipramine and clomipramine (TCAs); citalopram and escitalopram (SSRIs); diazepam (benzodiazepine) and partially for the biotransformation of venlafaxine and vilazodone. CYP2C9 is then responsible for the biotransformation of fluoxetine. Both CYP2C9 and CYP2C19 also contribute to the metabolism of sertraline and vortioxetine. In rats, maternal deprivation stress

caused an increased expression of CYP2C11 in the liver, however repeated restraint stress had no significant effect. There is a possibility that the stress-induced effect could be attributed to epinephrine, which induced CYP2C11 expression. In addition, the treatment of primary hepatocytes with corticosterone caused the upregulation of *CYP2C11* (ref.^{33,35}).

CYP2D6 is an important and well-studied CYP enzyme and highly expressed in the liver, brain, intestinal tissue and lymphoid cells. Although it constitutes only 2 – 4% of total CYP content in the liver, CYP2D6 is involved in the biotransformation of ~ 20% of drugs, including analgesics, antihypertensives, an anti-cancer agent (tamoxifen) and antidepressants such as nortriptyline, desipramine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, venlafaxine, duloxetine, vortioxetine, sertraline, and vilazodone⁴¹. It has been shown that psychological stress is able to modify hepatic CYP2D. In mice, restraint stress caused significant changes in the abundance of numerous hepatic proteins, including CYP2D22 (ref.³⁶). It also has been shown that exposure to repeated restraint stress upregulated the hepatic expression (mRNA and protein) of CYP2D1 in rats. This effect has been attributed to epinephrine⁹.

The CYP3A subfamily (mainly CYP3A4 isoenzyme) plays a major role in the metabolism of drugs (approximately 30%) and is able to catalyze the biotransformation of drugs from almost all therapeutic categories. The high sequence similarity between the CYP3A isoenzymes (CYP3A4 and CYP3A5 share more than 85% amino acid sequence identity) leads to similar substrate selectivity in the isoforms⁸. CYP3A isoenzymes participate in the metabolism of many antidepressants (such as clomipramine, citalopram, escitalopram, fluoxetine, sertraline, trazodone, nefazodone, vilazodone, vortioxetine) and anxiolytics (such as alprazolam, diazepam, midazolam, clonazepam, buspirone). In rats, maternal deprivation stress may be responsible for the modifications in their hepatic drug metabolism. It has been shown that CYP3A1/2 expression (mRNA and protein) was increased in the liver tissue of deprived rats in comparison to control mice. In addition, adult rats exposed to repeated restraint stress had an increased mRNA and protein level of CYP3A2, however CYP3A1 was not affected. The mRNA of CYP3A was also upregulated in murine liver^{33,36}. The stress-induced effect on CYP3A is mediated by epinephrine and glucocorticoids³⁵.

SELECTED ANTIDEPRESSANTS AND ANXIOLYTICS AND THEIR METABOLISM BY P450S

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) belong to a heterogeneous group of drugs, and they share a similar structure and a wide range of pharmacological effects with antipsychotics, such as chlorpromazine, which is an aliphatic phenothiazine⁴². Their common features are three central ring structures and a side chain (important for their

biological activity), which can be classified as a tertiary (amitriptyline, clomipramine, imipramine) or secondary (desipramine, nortriptyline) amine⁴³.

TCAs are mixed reuptake inhibitors of serotonin and noradrenaline, and they are also able to antagonize post-synaptic α_1 – adrenoceptors and histamine, serotonin and muscarinic cholinergic receptors. Nowadays, they are used to manage chronic pain, and to treat depression, obsessive-compulsive disorder, panic attacks, generalized anxiety disorder and post-traumatic stress disorder⁴³. Although TCAs are still prescribed and effective, they have poor tolerability and excessive side effects²⁰.

TCAs are mainly metabolized by CYP2C19 and CYP2D6, as the tertiary amines are metabolized by CYP2C19 to desmethyl metabolites - secondary amines with their own distinct clinical features. The CYP1A2 isoenzyme is also involved in the metabolism of TCAs, such as amitriptyline, clomipramine and imipramine⁴⁴. Amitriptyline is metabolized to nortriptyline, and imipramine is metabolized to desipramine by CYP2C19. CYP2D6 is then responsible for the metabolism of tertiary and secondary amines to less active metabolites⁴⁵. As the study shows⁴⁶, clomipramine can be not only metabolized by CYP2C19, but also by CYP1A2, CYP3A4 and CYP2D6.

Selective serotonin reuptake inhibitors (SSRIs)

The chemical structures of selective serotonin reuptake inhibitors (SSRIs) differ; some of them are tertiary amines (citalopram), some secondary amines (fluoxetine, sertraline and paroxetine) and some even primary amines (fluvoxamine) (ref.⁴⁷).

SSRIs are reuptake inhibitors of serotonin, so they can increase the availability of serotonin at the synapse⁴⁸. They are highly selective for the serotonin transporter (5-HT transporter), and are effective against most mood and anxiety disorders, however they are not without side effects²⁰. In contrast to TCAs, they can also be used to treat the elderly and children, and can be prescribed for patients with multiple comorbidities. SSRIs became the most prescribed antidepressants and drugs of choice to treat depression and anxiety, because of their overall efficacy, safety and tolerability¹⁹.

SSRIs are metabolized by a variety of CYPs. Citalopram exists as a racemate; there is R-citalopram and the biologically active S-citalopram, which is the active component of escitalopram (being an S-enantiomer of citalopram). Both enantiomers are metabolized by CYPs – mainly CYP2C19 and CYP3A4, with CYP2D6 playing a minor role, to R/S-demethylcitalopram, which is then converted to R/S-didemethylcitalopram⁴⁹. Fluvoxamine's chemical structure has no chiral center, and it is metabolized in the liver by CYP2D6 to its major (desmethoxy) metabolite⁵⁰. Fluoxetine, one of the most prescribed SSRIs in the world, is primarily metabolized via N-demethylation, mainly by CYP2D6, with contributions from CYP2C9 and CYP3A4. In addition, the contribution of CYPs to fluoxetine metabolism can vary, whereas fluoxetine exists as R-, S- or racemic fluoxetine⁵¹. Paroxetine is another antidepressant drug with promising therapeutic effects, and one of the most common off-label

drugs used in clinical practice. Its metabolism is mediated by CYP2D6 and CYP2B6, while also being an inhibitor of CYP2D6 (ref.⁵²). The final SSRI mentioned is sertraline, which is an effective drug used to treat depression and mania. The metabolism of sertraline via *N*-demethylation and deamination involves multiple enzymes, with CYP2B6 contributing to the greatest extent, and minor roles of CYP2C19, CYP2C9, CYP3A4 and CYP2D6 (ref.⁵³).

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine and duloxetine, which are serotonin and norepinephrine reuptake inhibitors (SNRIs), are other antidepressants used in the treatment of depression, anxiety and panic disorders. Compared to SSRIs, they have additional inhibitory activity at norepinephrine reuptake sites, however, their affinities for serotonin and norepinephrine transporters vary²⁰.

CYP2D6 is the main enzyme which catalyzes the biotransformation of SNRIs. Although venlafaxine is an SNRI, it is also able to weakly inhibit dopamine reuptake⁵⁴. Venlafaxine is metabolized by the hepatic CYP2D6 enzyme to its major active metabolite, *O*-desmethylvenlafaxine. Other CYPs can also participate in the metabolism of venlafaxine and its metabolite, namely CYP3A4 and CYP2C19, where less active metabolites are formed⁵⁵. Duloxetine, like venlafaxine, is an inhibitor of the reuptake of serotonin and norepinephrine, and has a weak effect on dopamine reuptake. In addition to the treatment of depression, it is also used in the treatment of stress urinary incontinence. Duloxetine is mainly metabolized to 4-, 5- and 6-hydroxy duloxetine by CYP2D6 and CYP1A2, which are the primary enzymes responsible for this oxidative metabolism followed by further oxidation, methylation and/or conjugation⁵⁶.

Serotonin antagonists and reuptake inhibitors (SARIs)

Trazodone and its analogue nefazodone are antidepressants which can inhibit both serotonin and norepinephrine reuptake, interact with α_1 -adrenoceptors, and do not interact with histaminergic or cholinergic receptors. They belong to a class of drugs called serotonin antagonists and reuptake inhibitors (SARIs) (ref.⁵⁷).

Trazodone is mostly used for its hypnotic and anxiolytic effects, and is often co-prescribed with other antidepressants as a sleep-inducing agent^{57,58}. It is extensively metabolized, undergoing hydroxylation, dealkylation and *N*-oxidation in the liver. Trazodone's psychopharmacologically active metabolite, *m*-chlorophenylpiperazine (mCPP), is formed (undergoing *N*-dealkylation) by the enzyme CYP3A4 (ref.⁵⁸). Nefazodone is a more potent antidepressant than trazodone, however it has been discontinued in many countries (in most European countries) mostly due to a possible side effect - causing severe and potentially fatal liver toxicity^{57,59}. Three active metabolites are formed from nefazodone - hydroxynefazodone, triazoledione and mCPP. All these metabolites are mainly formed by CYP3A4. mCPP as a psychoactive substance is further biotransformed into *p*-hydroxy-mCPP by CYP2D6 (ref.⁵⁹).

Norepinephrine and dopamine reuptake inhibitor (NDRI)

The norepinephrine and dopamine reuptake inhibitor (NDRI) bupropion is the only antidepressant with a dual effect on norepinephrine and dopamine neurotransmitter systems and no known serotonergic activity⁶⁰. In addition to the treatment of depression, bupropion is also an aid to stopping smoking or weight loss^{61,62}. Bupropion is extensively metabolized to hydroxybupropion by CYP2B6 in the liver. To a lesser extent, CYP1A2, 2A6, 2C9, 2D6, 2E1 and 3A4 also contribute to bupropion metabolism⁶¹.

Multimodal antidepressants (MMAs)

Vortioxetine and vilazodone belong to a class of novel antidepressant drugs called multimodal antidepressants (agents), and they combine multiple mechanisms of action.

Vortioxetine, used for the treatment of major depressive disorder, influences two different types of targets - serotonin receptors and transporters. Studies also suggest that vortioxetine may modulate serotonin, norepinephrine, dopamine, acetylcholine, histamine, glutamate and gamma-aminobutyric acid neurotransmitter systems. CYP2D6 is the primary enzyme for catalyzing the biotransformation of vortioxetine into a pharmacologically inactive metabolite. CYP3A4/5, CYP2A6, CYP2C9 and CYP2C19 are also involved in the breakdown of the parent compound. Oxidation via CYP enzymes is followed by glucuronic conjugation by enzymes of Phase II such as uridine diphosphate glucuronosyltransferase⁶³. Vilazodone combines the inhibition of selective serotonin reuptake and serotonergic receptor partial agonist activity, and does not affect norepinephrine or dopamine reuptake. The biotransformation of vilazodone is mainly via CYP3A4, with minor contributions from CYP2C19 and CYP2D6. It is also possible that carboxylesterase mediates non-CYP metabolism⁶⁴.

Anxiolytics - benzodiazepines and buspirone

Benzodiazepines were developed in the 1950s to replace the use of barbiturates, which have a narrower therapeutic index, are more sedative, and for which an overdose is more likely to be fatal^{23,65}. Benzodiazepines are so named because their core chemical structure consists of a benzene ring fused to a diazepine ring, and almost all of them also have a 5-aryl substituent ring. All their known actions are the results of effects mediated by the GABA receptor complex, and the main effects are sedation, hypnosis, decreased anxiety, and anterograde amnesia. Since their development, they have become drugs of choice in the treatment of anxiety⁶⁶. The main effects of benzodiazepines are sedation, hypnosis, decreased anxiety, anterograde amnesia, centrally mediated muscle relaxation, and anti-convulsant activity⁶⁷.

Alprazolam is a triazolobenzodiazepine and is widely used for the treatment of anxiety and panic disorders. Alprazolam is metabolized via CYP3A4 and CYP3A5 oxidation to 4-hydroxyalprazolam and α -hydroxyalprazolam, followed by glucuronidation⁶⁸. In addition to its use in anxiety treatment, diazepam's clinical uses include managing insomnia, muscle spasms, seizures, and alcohol

withdrawal. Diazepam is metabolized via CYP enzymes – CYP2C19 and CYP3A4, forming the major active metabolite desmethyldiazepam. The minor active metabolites, which are formed via CYP3A4 – temazepam and oxazepam, are usually not detectable⁶⁵. Midazolam is a benzodiazepine with a rapid onset (its distribution half-time is 6–15 min) and high plasma clearance. Firstly, midazolam is metabolized via CYP3A4 and CYP3A5 to form two pharmacologically active metabolites, α -hydroxymidazolam and 4-hydroxymidazolam. When

midazolam is present at sufficiently high concentrations, the formed α -hydroxymidazolam may significantly contribute to the effects of the parent drug, whereas 4-hydroxymidazolam is not important. Both metabolites are then rapidly conjugated by glucuronic acid to form pharmacologically inactive compounds⁶⁷. Clonazepam is an antiepileptic drug, structurally related to chlorthalidone hydrochloride, diazepam, and nitrazepam, and it has been used in the treatment of a variety of psychiatric disorders. Studies showed that clonazepam was able to

Table 1. CYP metabolism of selected antidepressants and anxiolytics with indications of potential effect of stress (\uparrow – increased and \downarrow – decreased expression/activity of CYP). Minor metabolic pathways are indicated in parenthesis. Individual drugs are divided into corresponding classes.

Class	Drug	Metabolism	Effect of stress on CYP	Ref.
Tricyclic antidepressants (TCAs)	Amitriptyline	CYP2C19 (CYP1A2)	\uparrow	43,44
	Nortriptyline	CYP2D6	\uparrow	43
	Imipramine	CYP2C19 (CYP1A2)	\uparrow	43,44
	Desipramine	CYP2D6	\uparrow	43
	Clomipramine	CYP2C19 (CYP1A2, CYP3A4)	\uparrow	72
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram	CYP2C19 CYP3A4 (CYP2D6)	\uparrow \uparrow	49
	Escitalopram	CYP2C19 CYP3A4 CYP2D6	\uparrow \uparrow \uparrow	48
	Fluvoxamine	CYP2D6 (CYP1A2)	\uparrow	50
	Fluoxetine	CYP2D6 CYP2C9 CYP3A4	\uparrow \uparrow \uparrow	51
	Paroxetine	CYP2D6 CYP2B6	\uparrow \downarrow	52
	Sertraline	CYP2B6 (CYP2C19, CYP2C9, CYP3A4, CYP2D6)	\downarrow	53
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine	CYP2D6 (CYP2C19, CYP3A4)	\uparrow	54,55
	Duloxetine	CYP2D6 CYP1A2	\uparrow ?	56
Serotonin antagonists and reuptake inhibitors (SARIs)	Trazodone	CYP3A4	\uparrow	58
	Nefazodone	CYP3A4	\uparrow	73
Norepinephrine and dopamine reuptake inhibitor (NDRI)	Bupropion	CYP2B6	\downarrow	61,74
Multimodal antidepressants (MMAs)	Vortioxetine	CYP2D6 (CYP3A4/5, CYP2A6, CYP2C19, CYP2C9)	\uparrow	63
	Vilazodone	CYP3A4 (CYP2C19, CYP2D6)	\uparrow	64
Benzodiazepines	Alprazolam	CYP3A4	\uparrow	75
	Diazepam	CYP3A4 CYP2C19	\uparrow \uparrow	65
	Midazolam	CYP3A4 CYP3A5	\uparrow	67
	Clonazepam	CYP3A4	\uparrow	70
Other	Buspirone	CYP3A4	\uparrow	71

reduce psychiatric symptoms in schizoaffective patients, suppress the psychotic symptoms of atypical psychosis, and successfully treat depression, as many investigators have reported that it may be used as an antidepressant⁶⁹. Clonazepam undergoes extensive biotransformation by nitro reduction catalyzed by CYP3A4, forming 7-amino-clonazepam, followed by further N-acetylation, which is catalyzed by N-acetyl transferase 2 (ref.⁷⁰).

Buspirone is an anxiolytic drug from the azapirone class. It was originally approved for the treatment of generalized anxiety disorder, but is also effective for the treatment of panic disorder, depression, obsessive-compulsive disorder and social phobia. Buspirone has fewer side effects (such as sedation and motor impairment) than the benzodiazepines. Its primary pharmacological action differs from the benzodiazepines, and is associated with binding to the serotonin subtype 1A receptor. Buspirone's major metabolic pathways consist of N-dealkylation, N-oxidation and hydroxylation. It was found that CYP3A4 is the primary enzyme that catalyzes the biotransformation of buspirone⁷¹.

CONCLUSIONS

The majority of psychoactive substances are metabolized by a limited number of liver microsomal enzymes. However, as the data on the effect of stress on human enzymes are extremely rare, modulation of the efficacy and even regulation of the biotransformation pathways of drugs by psychological stress can be expected to play a significant role. Available data on the metabolism of psychoactive drugs with indications of the effect of stress are summarized in Table 1. This aspect of pharmacotherapy hence deserves further attention in future studies.

Search strategy and selection criteria

Our aim was to provide an overview of the possible influence of psychological stress on the CYP metabolism of selected antidepressants and anxiolytics. Scientific articles were searched using the PubMed databases. All searches were up to date as of 2021. The search terms used included "metabolism of antidepressants", "metabolism of anxiolytics", "effect of stress on drug metabolism", "effect of psychological stress on cytochromes P450", "psychological stress", "drug metabolism".

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