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Review

The mechanisms of interactions of psychotropic drugs with liver and brain cytochrome P450 and their significance for drug effect and drug-drug interactions

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ABSTRACT

Cytochrome P450 (CYP) plays an important role in psychopharmacology. While liver CYP enzymes are responsible for the biotransformation of psychotropic drugs, brain CYP enzymes are involved in the local metabolism of these drugs and endogenous neuroactive substances, such as neurosteroids, and in alternative pathways of neurotransmitter biosynthesis including dopamine and serotonin. Recent studies have revealed a relation between the brain nervous system and cytochrome P450, indicating that CYP enzymes metabolize endogenous neuroactive substances in the brain, while the brain nervous system is engaged in the central neuroendocrine and neuroimmune regulation of cytochrome P450 in the liver. Therefore, the effect of neuroactive drugs on cytochrome P450 should be investigated not only *in vitro*, but also at *in vivo* conditions, since only *in vivo* all mechanisms of drug-enzyme interaction can be observed, including neuroendocrine and neuroimmune modulation.

Psychotropic drugs can potentially affect cytochrome P450 *via* a number of mechanisms operating at the level of the nervous, hormonal and immune systems, and the liver. Their effect on cytochrome P450 in the brain is often different than in the liver and region-dependent. Since psychotropic drugs can affect cytochrome P450 both in the liver and brain, they can modify their own pharmacological effect at both pharmacokinetic and pharmacodynamic level. The article describes the mechanisms by which psychotropic drugs can change the expression/activity of cytochrome P450 in the liver and brain, and discusses the significance of those mechanisms for drug action and drug-drug interactions. Moreover, the brain CYP2D6 is considered as a potential target for psychotropics.

1. Introduction

Cytochrome P450 (CYP) is a terminal oxidase in the mixed function oxidase system, mainly located in the endoplasmic reticulum of the liver, but also in other organs including the brain, where it is present in all cell membranes [1–6]. Cytochrome P450 consists of a great number of hemoprotein enzymes, which have been classified to families and subfamilies on the basis of amino acid sequence similarity and evolution process [7]. The families of CYP1-3 take part in the oxidative metabolism of xenobiotics (drugs, toxins, environmental pollutions), though they also metabolize endogenous substances, such as steroids. CYP families marked with higher numbers are responsible for the metabolism of essential endogenous substrates, e.g. cholesterol, arachidonic acid, steroids, fatty acids [8].

Cytochrome P450 plays an important role in psychopharmacology. While liver CYP enzymes are responsible for the biotransformation of psychotropic drugs, brain CYP enzymes are involved in the local metabolism these of drugs and endogenous neuroactive substances, such as neurosteroids and in alternative pathways of neurotransmitter biosynthesis including dopamine and serotonin [9]. The activity of cytochrome P450 may be changed by genetic polymorphism, exposure to xenobiotics (drugs, environmental pollutions) or at pathological conditions

Abbreviations: ACTH, adrenocorticotropic hormone; ARC, the arcuate nucleus; NMDAR, NMDA receptor; CAR, constitutive androstane receptor; CRH, corticotropin-releasing hormone; CYP, cytochrome P450; GH, growth hormone; GHRH, growth hormone-releasing hormone; GR, glucocorticoid receptor; IL-6, interleukin-6; IFNγ, interferon-γ; TNFα, tumor necrosis factor-α; TRH, thyrotropin-releasing hormone; PVN, the paraventricular nucleus; PXR, pregnane X receptor; TSH, thyroid-stimulating hormone; TGFβ, transforming growth factor-β.

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(inflammation, stress, nervous system disorders), which often leads to responses of physiological or pharmacological importance [10–15].

Studies of the last decade have revealed that there is a certain relation between the brain nervous system and cytochrome P450, i.e., CYP enzymes metabolize endogenous neuroactive substances in the brain, while the brain nervous system is engaged in the central neuroendocrine and neuroimmune regulation of cytochrome P450 in the liver. This kind of functional relation between the brain and cytochrome P450 seems to be implicated in psychotropic drug actions. Since psychotropics can affect cytochrome P450 in the liver and brain, they may modify their pharmacological effect at both pharmacokinetic and pharmacodynamic level. The article describes mechanisms by which psychotropic drugs can change the expression and activity of cytochrome P450 and discusses the significance of those mechanisms for drug action and drug-drug interactions.

2. The engagement of the brain nervous system in the regulation of liver cytochrome P450 by antidepressants and neuroleptics: A role of noradrenergic, dopaminergic, serotonergic and glutamatergic systems

To achieve and maintain the desired therapeutic effect in mental disorders, and to prevent relapses, psychotropic drugs have to be administered to patients for long time, which creates conditions for different types of interactions with cytochrome P450 (direct and indirect), and for development of adaptive changes within the brain nervous system, and in the hormonal and immune systems. All those events may be reflected in the activities of CYP enzymes.

Studies carried out on animals have shown that the brain monoaminergic systems (noradrenergic, dopaminergic and serotonergic) are important regulators of liver cytochrome P450 (Fig. 1). By acting on their receptors in the hypothalamic paraventricular nuclei (producing CRH, TRH, somatostatin), arcuate nuclei (producing GHRH) or in the pituitary gland (producing ACTH, TSH, GH), monoaminergic neurotransmitters stimulate or inhibit the secretion and plasma concentration of corticosterone, thyroid gland hormones (T_3, T_4) or growth hormone, respectively [16–20]. The mentioned hormones present in plasma regulate positively (CYP1A, CYP2B, CYP3A, 2C11 by corticosterone or CYP2C11 and CYP3A by growth hormone) or negatively (CYP1A, CYP2B, CYP2C6, CYP2C11 and CYP3A by thyroid hormones) cytochrome P450 expression and activity [21–23]. Thus, intracerebral administration of specific neurotoxins or agonist of monoaminergic receptors lead to changes in the neuroendocrine regulation of liver cytochrome P450 [19,20,24–29].

In general, the brain noradrenergic and dopaminergic systems positively regulate CYP2B, CYPC11 and CYP3A enzymes (*via* α_2 and D_2 receptors, respectively), while the serotonergic system negatively regulate those enzymes (*via* 5-HT_{1A} receptors) [25,26,30]. All the three brain monoaminergic systems negatively regulate CYP1A. However, different effects may be observed after local administration of specific neurotoxins or monoaminergic receptor agonists to the hypothalamic paraventricular or arcuate nuclei, since the paraventricular and arcuate nuclei exert opposite effects on the secretion of growth hormone due to the action of somatostatin or GHRH, respectively [17,18]. For example, the stimulation of 5-HT_{1A} receptors in the paraventricular nuclei decreases the expression and activity of CYP2C11 and CYP3A enzymes (*via* somatostatin-GH and corticosterone pathway), while the stimulation of 5-HT_{2C} receptors in the arcuate nuclei increases the expression and activity of CYP2B, CYP2C11 and CYP3A (*via* GHRH-GH pathway) in rat liver [19,31]. An important role of the brain monoaminergic systems in the neuroendocrine regulation of liver cytochrome P450 has been reviewed [25,30]. Recent studies suggest that the brain glutamatergic system may also contribute to positive neuroendocrine regulation of cytochrome P450 *via* NMDA receptor and hormonal pathways engaging growth hormone and corticosterone [32]. Such neuroendocrine regulation was observed after 5-day treatment with the selective NMDA receptor GluN2B subunit antagonist CP-101,606 (a decrease in CYP2C11 and CYP3A expression and activity at a diminished GHRH, GH and corticosterone levels). The effect was less pronounced after 3-week treatment, which suggest adaptive changes in the neuroendocrine system. The applied ligands of metabotropic glutamatergic receptors (mGluR) were not active in this respect [33].

The above-mentioned neuroendocrine mechanisms may be involved in the regulation of cytochrome P450 by neuroactive drugs including

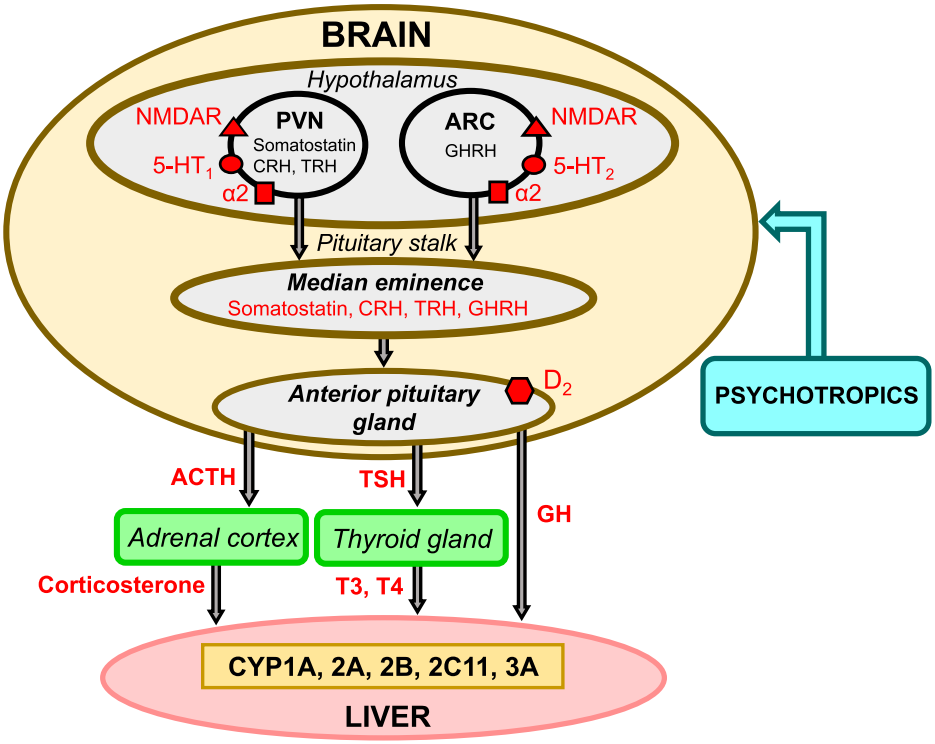

Fig. 1. Neuroendocrine regulation of liver cytochrome P450 by brain neurotransmitters. By acting on neurotransmitter receptors present in the hypothalamic paraventricular and arcuate nuclei, neuroactive drugs influence the secretion of releasing (CRH, TRH, GHRH) or inhibiting (somatostatin) hormones, and as a result, the secretion of respective pituitary hormones: ACTH, TSH or GH. Moreover, neurotransmitter receptors present in the pituitary gland also affect hormone secretion (D_2 receptor stimulation of GH secretion). The secreted pituitary, adrenal and thyroid hormones regulate positively (glucocorticoids, GH) or negatively (T_3 and T_4) the expression of related *CYP* genes in the liver. PVN, the paraventricular nucleus; ARC, the arcuate nucleus; NMDAR, NMDA receptor; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; GHRH, growth hormone-releasing hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; GH, growth hormone.

psychotropics, as well. Prolonged administration of agomelatine (a 5-HT_{2C} antagonist) in the animal model of depression decreased the expression and activity of CYP2C11 and CYP3A, while increased that of CYP1A [34]. The atypical neuroleptics asenapine and iloperidone (antagonists of D_2 and 5-HT_2 receptors) given for 2 weeks reduced the expression and activity of CYP1A, CYP2B, CYP2C11 and CYP3A enzymes in rat liver [35,36].

Thus, the effect of neuroactive drugs on cytochrome P450 should be investigated not only *in vitro*, but also at *in vivo* conditions, since *in vivo* all mechanisms of drug-enzyme interaction can be observed, including neuroendocrine and neuroimmune modulation [37,38]. Apart from hormones, cytokines are also important physiological/pathological regulators of CYP-enzymes [10,13,39]. The secretion of cytokines can be regulated by the brain nervous system (*via* hormonal and autonomic nervous systems) and *via* neurotransmitter receptors present on immune cells in the blood (Fig. 2). The concentration of proinflammatory cytokines in blood plasma increases in stress and depression and declines after antidepressant treatment [40–44]. Changes in plasma cytokine concentration occur also in schizophrenic patients, however, a relation between particular cytokine levels, schizophrenia and neuroleptic treatment seems less clear than in depression [39,45–49]. In any case, those alterations in plasma cytokine concentrations in the course of mental disorders and pharmacotherapy may be reflected in alterations in CYP enzymes' levels and activities [39].

However, the effects evoked by drug action on brain receptors and central neuroendocrine or neuroimmune regulation of liver cytochrome P450 may be in some cases masked by drug action at the level of the liver (Fig. 3). For instance, imipramine induces the expression of liver CYP3A, but it does not increase its activity *in vivo*, since the antidepressant produces reactive metabolites, which form irreversible CYP-iron-complexes and inactivate the enzyme [34,50]. Moreover, imipramine and other psychotropic drugs are known to reversibly bind to CYP enzyme proteins, so the final effect *in vivo* will be a resultant of those three mechanisms, i.e., binding to CYP3A, formation of CYP3A-reactive metabolite complexes and CYP3A gene regulation, and will depend on an actual drug concentration in the liver (reviewed in [51]).

3. The involvement of the mechanisms operating in the liver in the effects of psychotropics on cytochrome P450: Binding to the enzyme, inhibition by reactive metabolites and regulation of *CYP* gene expression

Psychotropic drugs are substrates of cytochrome P450, so they bind to the catalytic site of the enzyme and compete with other substrates for this site. CYP2D6, CYP3A4 and CYP2C are the main enzymes catalyzing aromatic hydroxylation and N-demethylation reactions of those drugs (reviewed in [12,51]). As mentioned before, psychotropic drugs are known to reversibly bind to CYP enzymes and inhibit CYP activity *via* competitive, non-competitive or mixed mechanism. Tricyclic antidepressants (TADs) and selective serotonin reuptake inhibitors (SSRIs) are known inhibitors of human CYP2D6 and rat CYP2Ds [51]. Moreover, fluvoxamine is a strong inhibitor of CYP1A2, CYP2C19 and CYP3A4, fluoxetine is a CYP2C19 inhibitor, while norfluoxetine is a CYP3A4 inhibitor [52]. Phenothiazine neuroleptics, haloperidol or older atypical antipsychotics may also directly inhibit the activity of CYP enzymes [51]. For example, levomepromazine and clozapine are inhibitors of CYP2D6 and, to a lesser extent, of CYP1A2, CYP2C9 and CYP3A4 [53,54]. Recent studies indicate that the novel atypical neuroleptics can also inhibit CYP enzymes: asenapine inhibits CYP1A2 and CYP2D6, iloperidone inhibits CYP3A4, CYP2C19 and CYP2D6, while lurasidone is a moderate inhibitor of CYP1A2, CYP2C9 and CYP219 enzymes (Table 1) [55,56].

On the other hand, some psychotropics, such as tricyclic antidepressants, phenothiazine neuroleptics or haloperidol produce reactive metabolites, which irreversibly bind to CYP enzymes, in this way inhibiting enzyme activity (Fig. 3). Tricyclic antidepressants and fluoxetine have been shown to form inhibitory CYP-iron(II)-nitrosoalkane metabolite complexes, affecting CYP3A, CYP2C11 and CYP2A [57,58]. Likewise, epoxide intermediates of imipramine (and probably of other antidepressants) formed during hydroxylation process, radical cations of phenothiazine neuroleptics mediating their sulfoxidation and ring hydroxylation, and haloperidol pyridinium metabolites (HPP^+) irreversibly inhibit CYP2D6 activity [51,59,60]. The

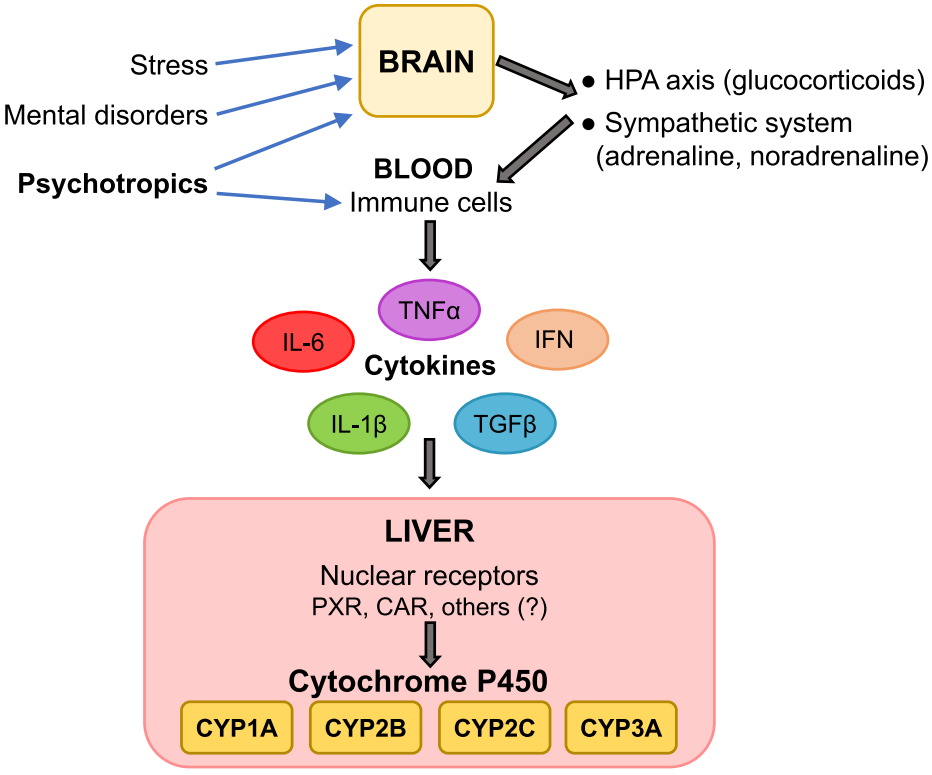

Fig. 2. Neuroimmune regulation of liver cytochrome P450. The central neuroimmune regulation of liver CYP enzymes proceeds throughout the hormonal HPA axis (*via* glucocorticosteroids produced by the adrenal gland cortex) and autonomic sympathetic system (*via* adrenaline and noradrenaline released by the adrenal gland medulla). Both glucocorticosteroids and catecholamines act on their receptors present on immune cells and regulate the secretion of cytokines. By negative regulation of nuclear receptor expression (PXR, CAR), cytokines (IL-1β, IL-6, TNFα, TGFβ, IFNγ) negatively regulate cytochrome P450 enzymes in the liver. Moreover, neuroactive drugs can directly act on neurotransmitter receptors located on immune cells. HPA axis, the hypothalamus–pituitaryadrenal axis; PXR, pregnane X receptor; CAR, constitutive androstane receptor; IL-1β, interleukine-1β; IL-6, interleukine-6; TNFα, tumor necrosis factor-α; IFNγ, interferon-γ; TGFβ, transforming growth factor-β.

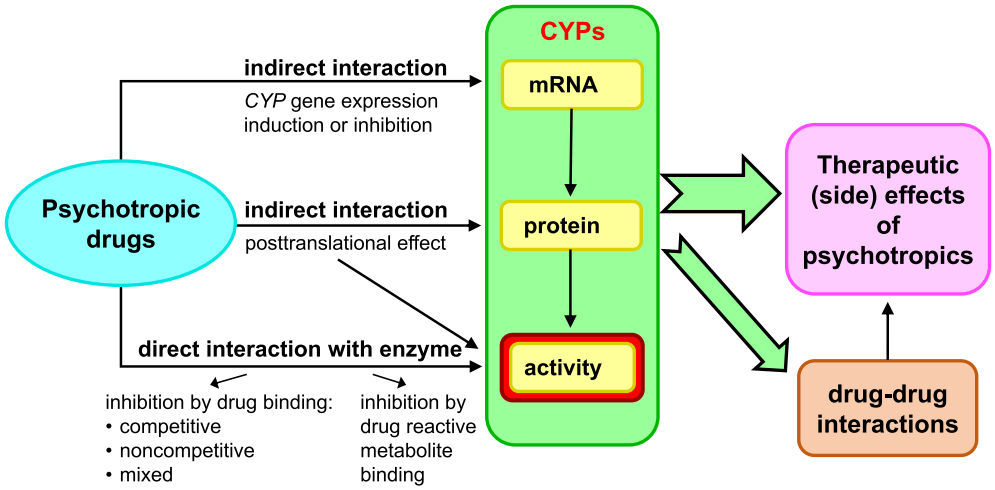

Fig. 3. Various mechanisms of interaction of psychotropic drugs with cytochrome P450 at the level of liver during long-term treatment. Drugs can affect the expression of *CYP* genes and produce posttranscriptional or posttranslational alterations in enzyme biosynthesis and function. Drugs and their metabolites can also bind to enzyme protein in reversible or irreversible manner.

formation of above irreversible CYP-reactive metabolite complexes was observed in rat and human liver microsomes *in vitro* and was confirmed in animal experiments *in vivo* [50,61–63].

Another mechanism by which psychotropics can influence cytochrome P450 at the level of the liver is related to their influence on the enzyme expression (Fig. 3). *In vitro* studies using human hepatocytes showed that, when added to the cell culture, levomepromazine and the atypical neuroleptics clozapine, asenapine and iloperidone affected *CYP* mRNA levels and activity of respective enzymes (Table 1). Levomepromazine and clozapine increased the mRNA level and activity of the main CYP enzyme in human liver, i.e., CYP3A4 with no changes in CYP1A1/2, CYP2C9 and CYP2C19 [64]. In contrast, asenapine decreased the *CYP1A2* mRNA level and activity, iloperidone diminished those of CYP3A4, while lurasidone did not affect the expression or activity of the investigated CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP3A4) [65]. Considering the involvement of cytoplasmic receptor AhR in the expression of *CYP1A2*, the engagement of nuclear receptors PXR, CAR and RXR in the expression of *CYP3A4* (as well as *CYP2C9* and *CYP2C19*), and a role of GR in the expression of all the investigated CYP enzymes, it can be deduced that asenapine interacts with AhR, whereas clozapine and iloperidone do not act as direct ligands of the nuclear receptors PXR or CAR, which are engaged in the transcriptional regulation of both CYP3A and CYP2C genes [66–68]. The investigated neuroleptics do not seem to interact with GR, either. So, their mechanism of enzyme induction/inhibition at the level of the liver needs further molecular investigation. Interestingly, chlorpromazine is considered as an agonist of mouse CAR, but its effect on human CAR has not been shown [69–71].

Moreover, there are adrenergic (α_1 and β_2) and serotonergic (5-HT_2) receptors in the liver, which *via* an appropriate signal transduction pathway stimulate phosphorylation of nuclear transcription factors that regulate the expression of hepatic genes, including *CYP* genes [13,72,73]. Neurotransmitter receptors (adrenergic, dopaminergic, serotonergic and others) are also present on immune cells, where they regulate the release of cytokines, which control the expression of nuclear receptors and, in turn, liver *CYP* genes' expression [23,39]. Muntané-Relat et al. [74] discovered that interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) strongly repressed *CYP3A* and *CYP1A* genes, respectively in human hepatocytes. Latter studies carried on human hepatocytes showed that the expression of cytochrome P450 enzymes responded independently to inflammatory cytokines. CYP3A4 and CYP2C8 were down-regulated by IL-1β, IL-6, TNFα, interferon-γ (IFNγ) and transforming growth factor-β (TGFβ). CYP2C9 and CYP2C19 were down-regulated by IL-6 and TGFβ, while CYP2B6 by IL-6 and IFNγ [75,76]. Similar results were obtained in rabbit hepatocytes [77]. Another investigation revealed that proinflammatory cytokine IL-1β decreased the expression of constitutive androstane receptor (CAR), while IL-6 negatively regulated the expression of pregnane X receptor (PXR) in human hepatocytes [78,79]. Many other cytokines can also affect the expression of cytochrome P450 enzymes [39].

Thus, apart from the central neuroimmune regulation of plasma cytokine concentrations engaging the brain nervous system (evoked by stress, mental disorders or psychopharmacotherapy), independent peripheral regulation of cytokine levels *via* direct action of psychotropics on immune cell receptors in the blood is also possible. Those two mechanisms are important for the expression of cytochrome P450 in the liver, and probably in other organs (Fig. 2).

The above described possibilities of psychotropic drug action on liver cytochrome P450 (chapters 2 and 3) indicate that these drugs can affect the enzyme activity *via* following mechanisms: 1) direct action of drugs and their metabolites on the enzyme protein (binding); 2) influence on *CYP* gene expression at the level of the liver; 3) central neuroendocrine regulation of liver *CYP* gene expression *via* brain neurotransmitter systems and hormonal pathways; 4) central neuroimmune regulation of liver *CYP* by engaging the HPA axis (and glucocorticoids produced by the adrenal gland cortex) and autonomic sympathetic system (and adrenaline/noradrenaline released by the adrenal gland medulla); and 5) direct action of psychotropics on neurotransmitter receptors present on immune cells, which regulate the release of cytokines (Fig. 4). Those five mechanisms may operate at the same time during long lasting psychopharmacotherapy and lead to different metabolic (pharmacokinetic) interactions between psychotropic drugs, as well as between psychotropics and other concomitantly administered drugs. A number of metabolic interactions have been found in the clinical combinations of psychotropics. For example, neuroleptics have been shown to decrease the activity of liver CYP2C and CYP3A enzymes and increase plasma concentrations of tricyclic antidepressants after chronic treatment. However, the mechanisms of those interactions have not been fully recognized so far, since only mechanisms operating at the level of the liver were considered and demonstrated (reviewed in [23,51]). Therefore, further appropriately designed *in vivo* studies are necessary to find out to what extent processes operating in the brain contribute to metabolic/pharmacokinetic interactions produced by psychotropics.

While direct effects of psychotropic drugs on cytochrome P450 activity at liver level (*via* binding to CYP enzymes or interacting with CYP gene expression) have been experimentally proven, the psychotropic effects on the expression of cytochrome P450 *via* neuroendocrine and

Table 1
The influence of neuroleptics on cytochrome P450 (CYP) activity in human liver microsomes and on the CYP activity and mRNA level after 72 h-exposure of human hepatocytes to the drugs.

Drugs	Liver microsomes (K_i [μM], inhibition type)	Hepatocytes		References
		Activity	mRNA level	
Levomepro-mazine	**CYP1A2**[a] (47, mixed) **CYP2D6**[a] (6, competitive) **CYP3A4**[a] (34, mixed)	— n.t. ↑	— n.t. ↑	[53, 64]
Clozapine	**CYP2C9** (31, competitive) **CYP2C19** (69, competitive) **CYP2D6** (19, competitive) **CYP3A4** (99, noncompetitive)	— — n.t. ↑	— — n.t. ↑	[54, 64]
Asenapine	**CYP1A2** (3.2, mixed) **CYP2D6** (1.75, competitive) **CYP3A4** (31.3, noncompetitive)	↓ n.t. —	↓ n.t. —	[56, 65]
Iloperidone	**CYP1A2** (45, mixed) **CYP2C19** (6.5, mixed) **CYP2D6** (2.9, competetive) **CYP3A4** (0.38, noncompetitive)	— — n.t. ↓	— — n.t. ↓	[55, 65]
Lurasidone	**CYP1A2** (12.6, mixed) **CYP2C9** (18, mixed) **CYP2C19** (18, mixed) **CYP2D6** (37.5, competiyive) **CYP3A4** (29.4, competitive)	— — — n.t. —	— — — n.t. —	[55, 65]

n.t. – not tested; — – no effect; ↑,↓ – increase or decrease, respectively; [a]– tested using human cDNA-expressed CYPs (Supersomes).

neuroimmune mechanisms are hypothetical to some extent, and yet to be investigated. They are based on the following clear evidence: (1) the action of psychotropics on the neurotransmitter systems in the brain and on neurotransmitter receptors present on immune cells or hepatocytes; (2) the effects of neurotransmitter receptors (and psychotropics as well) on the endocrine and immune systems; (3) the effects of endocrine/immune systems on CYP enzyme regulation; and (4) the effects of prolonged administration of psychotropic drugs on *CYP* gene expression, which positively correlate with hormonal changes produced by psychotropics. However, the described here possible neuroendocrine and neuroimmune mechanisms of cytochrome P450 regulation by psychotropic drugs need further experimental confirmation.

4. The effect of psychotropic drugs on brain cytochrome P450: A physiological role of CYP2D enzymes in the brain, the effect of antidepressants and neuroleptics on CYP2D in different brain regions and its possible role in their pharmacological effect

Brain cytochrome P450 takes part in the metabolism of endogenous substrates and local biotransformation of drugs. Among CYP enzymes, CYP2D6 seems to be particularly meaningful, because of its significant role in the biotransformation of psychotropic drugs [12,51,80] and the ability to synthesize neurotransmitters, such as dopamine and serotonin, as well as to metabolize neurosteroids [9,81]. Therefore, the influence of psychotropics on the activity of this enzyme may be of pharmacological importance (Fig. 5).

In vitro studies using cDNA-expressed CYP2D6 or liver microsomes revealed that CYP2D6 can catalyze the formation of dopamine and serotonin *via* tyramine hydroxylation or 5-methoxytryptamine *O*-demethylation, respectively [82,83]. The *in vitro* comparative studies showed that the efficiency of human CYP2D6 in synthesizing dopamine and serotonin was much higher compared with rat CYP2Ds, and the occurrence of these reactions in brain microsomes was evidenced [84,85]. *In vivo* studies demonstrated the CYP2D-mediated synthesis of dopamine from endogenous and exogenous tyramine, and serotonin formation from exogenous 5-methoxytryptamine in rat brain using the brain microdialysis model [86–88]. Moreover, an increased serotonin level in the brain of CYP2D6-transgenic mice was shown by Cheng et al. [89]. However, the relative contributions of those alternative pathways to the total neurotransmitter synthesis in human brain *in vivo* require further investigation (discussed in [9,15,90]. Human CYP2D6 and rat CYP2D1 and CYP2D4 enzymes have also been shown to catalyse 21-

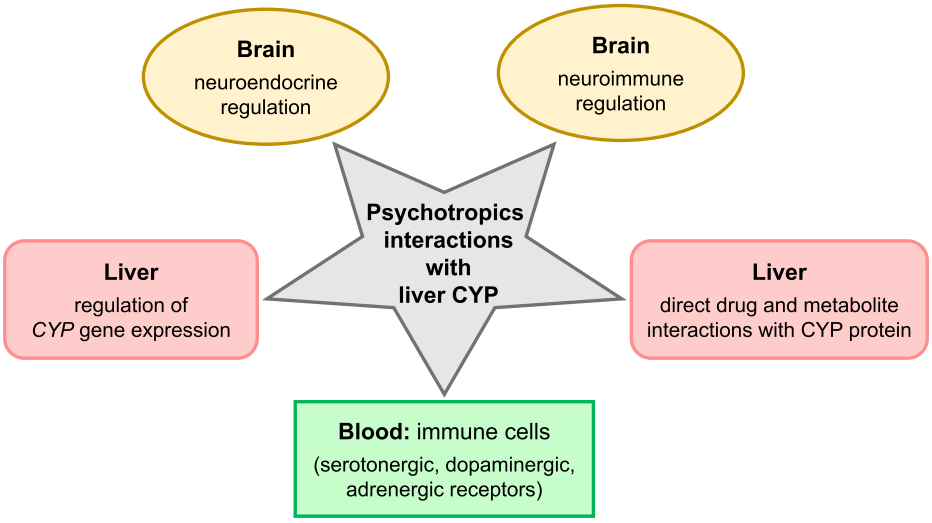

Fig. 4. The main stages and mechanisms of psychotropic drug action on liver cytochrome P450. Psychotropics can influence the expression and activity of liver CYP enzymes by exerting their action not only in the liver, but also throughout other organs or tissues (brain, blood), including different mechanisms.

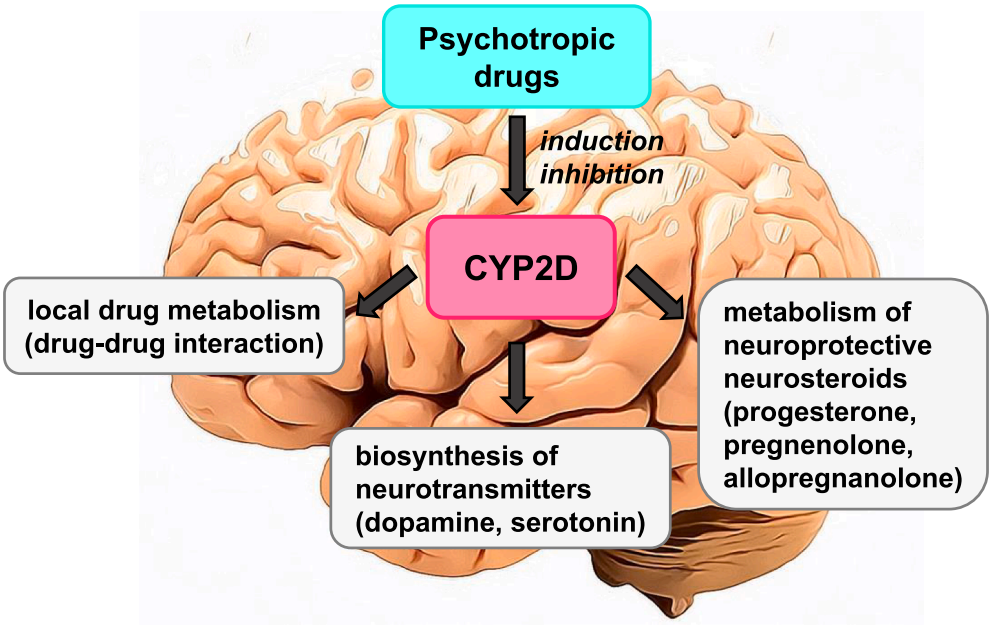

Fig. 5. The effects of psychotropic drugs on local CYP2D-mediated metabolism in the brain. New additional mechanisms of pharmacological action of psychotropic drugs. By acting on the CYP2D enzymes in the brain, psychotropics can affect its own local biotransformation and the metabolism of endogenous neuroactive substances (dopamine, serotonin, neurosteroids).

hydroxylation of neurosteroids, using cDNA-expressed CYP2Ds and brain microsomes [81,91–93]. Those enzymes oxidized neuroprotective neurosteroids including progesterone, pregnenolone and allopregnanolone in brain microsomes, and the reaction was inhibited by imipramine, desipramine and fluoxetine.

Brain cytochrome P450 was shown to contribute to the biotransformation of neuroactive drugs, and to affect their local concentrations and central pharmacological/toxicological responses (reviewed in [94]). Changes in the activity of brain CYP2D and metabolism of haloperidol affect the acute and chronic side-effects of this drug measured in the rat behavioral models, and may be a risk factor for antipsychotic side-effects after acute (e.g. parkinsonism) or chronic (e.g. tardive dyskinesia) neuroleptic treatment [95]. Regulation of cerebral CYP2D activity by nicotine (inducer) or propranolol (inhibitor) alters brain metabolism and analgesic effect of codeine or tramadol [96–98]. Brain CYP2B significantly contributes to the local metabolism of the anaesthetic propofol and nicotine, which correlates with behavioral effects [99,100].

Brain cytochrome P450 enzymes are often regulated differently than their liver counterparts, and in a region-dependent manner, which may result from differences in the levels of nuclear receptors and transcription factors regulating *CYP* genes between the brain and the liver, and between particular brain regions [101]. Individual brain structures contain different neuronal cell types possessing various receptors and receiving peculiar afferent innervations which provide intracellular signals affecting protein phosphorylation and function (including nuclear receptors, transcription factors and enzyme proteins), and gene expression. It also may be a reason for regional differences in the regulation of CYP enzymes in the brain [90]. On the other hand, the blood–brain barrier does not allow for free penetration of all

endogenous substances, drugs and their metabolites formed in the liver from periphery to the brain, which may be an additional reason for different regulation of cytochrome P450 in the two organs by psychotropics.

Thus, *in vivo* studies showed that the effect of psychotropic drugs on brain CYP2D activity after chronic treatment was different than in the liver and was brain region dependent (Table 2) [102,103]. As in the liver, fluoxetine diminished the CYP2D activity in the striatum and nucleus accumbens, but increased it in the cerebellum. The inhibition of CYP2D activity by antidepressants may slow the metabolism of neurosteroids and increase their concentration in the brain, improving in this way the pharmacological effect of antidepressants in depressive patients, as suggest by clinical observations [104–110]. Nefazodone decreased the CYP2D activity in the liver, but increased in the brain stem, which is the structure containing both serotonergic neurons of the raphe nuclei and dopaminergic neurons of the ventral tegmental area [103]. The latter effect may be beneficial for antidepressant therapy, since by increasing CYP2D activity in the brain stem, nefazodone may accelerate serotonin regeneration from 5-methoxytryptamine and tyramine hydroxylation to dopamine, while both neurotransmitters are known to be involved in depression (discussed in [102]).

Our study on CYP2D, performed in the chronic mild stress (CMS) paradigm, a rat model of depression, showed that CMS significantly increased the brain CYP2D activity in the hippocampus without affecting the enzyme in other brain structures or in the liver [111]. Chronic treatment with escitalopram or venlafaxine significantly elevated the enzyme activity in the frontal cortex, hypothalamus and cerebellum in stressed rats, but not in non-stressed animals. It suggests that CMS triggers the stimulatory effect of the antidepressants on the CYP2D activity, thereby regulating the metabolism of some endogenous substances playing an important role in depression, like serotonin or dopamine.

Chronic treatment with neuroleptics also showed regional differences in the effect of chronic drug administration on brain CYP2D. Prolonged administration of thioridazine decreased the protein level/activity of CYP2D in the nucleus accumbens and liver, but enhanced it in the striatum and cerebellum, while in the substantia nigra the activity decreased though protein level rose [103]. On the other hand, clozapine, which did not affect the CYP2D in the liver, produced many changes in the brain: a decrease in the enzyme activity and protein level in the nucleus accumbens and substantia nigra, but an increase in the bulbus olfactory, brain stem and cerebellum [102,103,112].

Our recent studies with the atypical neuroleptics asenapine and iloperidone showed regional differences in the drug effect on brain CYP2D, as well. Two-week treatment with asenapine diminished the activity and protein level of CYP2D in the liver, frontal cortex, nucleus accumbens, hippocampus and cerebellum, but did not affect the enzyme in the hypothalamus, brain stem, substantia nigra [113]. In contrast, asenapine enhanced the CYP2D activity and protein level in the striatum. Prolonged administration of iloperidone decreased the activity, protein and mRNA levels of CYP2D1, CYP2D2 and CYP2D4 in the liver. Similarly, iloperidone reduced the CYP2D activity and protein levels in the frontal cortex and cerebellum, but enhanced those levels in the nucleus accumbens, striatum and substantia nigra. Chronic iloperidone did not change the brain levels of CYP2D4 mRNA (the main rat CYP2D enzyme), except in the striatum, where that level was enhanced [114], which points to posttranscriptional and transcriptional mechanism of the brain CYP2D4 regulation, respectively, by the neuroleptic. The above results suggest that by acting on brain CYP2D the applied atypical neuroleptics may modify their pharmacological effect. By inducing the CYP2D activity in the nigrostriatal pathway they accelerate the synthesis of dopamine and thus attenuate extrapyramidal symptoms, while by reducing the enzyme activity in other brain regions (the frontal cortex, hippocampus, cerebellum) they slow the metabolism of neurosteroids, which may improve cognitive responses and exert a positive influence on the treatment of schizophrenia.

Molecular mechanisms of the regulation of brain *CYP2D* genes are not well known. Studies carried out in female rats indicated the regulation of brain CYP2D mRNA by steroid hormones [115,116]. The latter studies indicated that brain CYP2D might be down-regulated by sex hormones *via* miRNAs [117]. Using the SH-SY5Y human neuroblastoma cell line Zhang et al. [118] showed that the PPARγ receptor activated the *CYP2D6* gene promoter, while PPARα suppressed *CYP2D6* gene expression. Pulsatile GH treatment decreased the PPARα mRNA level and increased the mRNA levels of *CYP2D6* and PPARγ in SH-SY5Y human neuroblastoma cells. However, pulsatile pituitary GH, which is

Table 2
The effects of psychotropic drugs on the CYP2D activity and protein level in the liver and brain structures.

Drugs	Liver	FCx	St	NA	Hp	Ht	BS	SN	CB	RM	References
Asenapine	⇓⇩	⇓⇩	⇑⇧	⇓⇩	⇓⇩	—	—	—	⇓⇩	—	[113]
Iloperidone	⇓⇩	⇓⇩	⇑⇧	⇑⇧	—	—	—	⇑⇧	⇓⇩	—	[114]
Clozapine	—	—	—	⇓⇩	nt	nt	⇑⇧	⇩	⇧	⇑⇧	[103]
Thioridazine	⇓	—	⇑⇧	⇓⇩	nt	nt	—	⇓⇧	⇑⇧	—	[103]
Imipramine	⇓	—	—	—	nt	nt	—	—	—	—	[103]
Fluoxetine	⇓	—	⇓⇩	⇓⇩	nt	nt	—	—	⇑⇧	—	[103]
Mirtazapine	⇑	—	—	—	nt	nt	—	—	—	—	[103]
Nefazodone	⇓	—	—	—	nt	nt	⇑	—	—	—	[103]

⇓,⇑ – increase or decrease of activity, respectively; ⇧,⇩ – increase or decrease of protein level, respectively; — – no effect; n.t. – not tested. FCx – frontal cortex, St – striatum, NA – nucleus accumbens, Hp – hippocampus, Ht – hypothalamus, BS – brain stem, SN – substantia nigra, CB – cerebellum, RM – rest of brain.

released to the blood, does not easily penetrate the blood–brain barrier [119,120]. It seems therefore that *in vivo* the GH effect on neuronal CYP2D would rather depend on locally synthesized GH in the brain.

Yet, CYP2D enzymes may be regulated at the posttranscriptional level to increase protein stability or to decrease enzyme degradation, as suggested. For many xenobiotics, such as nicotine, alcohol or iloperidone posttranscriptional mechanisms of brain CYP2D modification have been suggested [101,114,121]. Direct interactions of psychotropic drugs with CYP2D enzymes in the brain (binding to the enzyme) seem to be less important than in the liver, because of high unspecific drug binding in brain tissue, which leads to greater K_i values as shown for antidepressant and neuroleptics added to brain and liver microsomes [100,101,111,112].

It is nevertheless, very important that CYP2D6 is a polymorphic enzyme, so its activity is also regulated genetically [122,123]. About 7–10% of Caucasian populations exhibit CYP2D6 enzyme deficiency, while about 7–10% of inhabitants in European Mediterranean area display duplication or multiplication of *CYP2D6* gene [124]. Clinical observations suggest that CYP2D6 polymorphism may affect personality traits [125–128], and recent studies carried out in humans and animals indicate that the level of CYP2D activity may affect anxiety level, cognitive, learning and memory processes [89,118,129,130], and has an impact on drug-associated dizziness [131]. Moreover, the activity of CYP2D enzymes in the brain changes in a region-dependent manner during aging process in humans and rats, as well as under serotonin deficiency in male and female rats, indicating sex-differences in the effects of both aging and neurotransmitter deficiency on the expression and activity of those enzymes [15,132,133].

It suggests that selective targeting of CYP2D6 in particular brain areas engaged in pathology of mental and neurological disorders, could provide an additional component of pharmacological action of psychotropics, both in the aspect of improving therapeutic outcome and attenuation of side-effects. This, however, requires further research into the mechanisms of regulation of brain CYP enzymes.

5. Conclusions

The presented data emphasize the significance of the interplay between the brain nervous system and cytochrome P450 for the pharmacokinetics and pharmacological effect of psychotropic drugs, and for drug-drug interactions. Research of the last decade has revealed that there are several different mechanisms of interactions between psychotropic drugs and cytochrome P450. Apart from a direct interaction of drugs and their metabolites with CYP protein or *CYP* gene expression at the level of the liver, indirect interactions at the level of the brain (*via* endocrine, immune and autonomic nervous system) are also possible. The contribution of those mechanisms to the regulation of CYP enzyme activity in the liver may be changing in the course of psychopharmacotherapy, depending on the aetiology and phase of illness, time of treatment and actual drug concentration.

Recent studies show mutual interactions between cytochrome P450 and the brain function, namely the interaction between the brain nervous systems and liver cytochrome P450 at the level of central neuroendocrine and immune regulation, and between brain cytochrome P450 and monoaminergic neurotransmitters at the level of their local biosynthesis. By applying intracerebral administration of specific pharmacological tools it was found that the brain monoaminergic systems (dopaminergic, noradrenergic, serotonergic) and glutamatergic system affected cytochrome P450 enzyme expression and activity (CYP1A, CYP2A, CYP2B, CYP2C, CYP3A) in the liver *via* influencing hypothalamic (paraventricular and arcuate nuclei) and pituitary hormonal status. It indicates that it is vital to apply *in vivo* experimental models in order to discover a full spectrum of drug effect on liver cytochrome P450 and, in this way, to identity a risk of pharmacokinetic (metabolic) drug-drug interactions with neuroactive drugs at the level of the brain. On the other hand, it has been proven that brain cytochrome CYP2D enzymes catalyze alternative pathways of neurotransmitter synthesis (tyramine hydroxylation to dopamine and 5-methoxytryptamine *O*-demethylation to serotonin), as shown *in vitro* in brain microsomes and *in vivo* in the brain microdialysis model.

Psychotropic drugs affect cytochrome P450 *via* a number of mechanisms and their effect on cytochrome P450 in the brain is often different than in the liver and brain region dependent.

Psychotropic drugs influence the CYP2D activity in the brain, including the structures involved in the pathology of mental and neurological disorders, and in therapeutic action and side-effects of those drugs. Therefore, they can modify their own pharmacological effect. It suggests that selective targeting of CYP2D6 in particular brain areas could provide an additional component of pharmacological action of psychotropics. The latest research achievements open a new direction of searching for novel pharmacological targets based on brain cytochrome P450, for the treatment of neurological and psychiatric diseases.

CRediT authorship contribution statement

Władysława A. Daniel: Conceptualization. **Ewa Bromek:** . **Przemysław J. Danek:** . **Anna Haduch:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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