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REVIEW ARTICLE

The engagement of brain cytochrome P450 in the metabolism of endogenous neuroactive substrates: a possible role in mental disorders

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ABSTRACT

The current state of knowledge indicates that the cerebral cytochrome P450 (CYP) plays an important role in the endogenous metabolism in the brain. Different CYP isoenzymes mediate metabolism of many endogenous substrates such as monoaminergic neurotransmitters, neurosteroids, cholesterol, vitamins and arachidonic acid. Therefore, these enzymes may affect brain development, susceptibility to mental and neurodegenerative diseases and may contribute to their pathophysiology. In addition, they can modify the therapeutic effects of psychoactive drugs at the place of their target action in the brain, where the drugs can act by affecting the metabolism of endogenous substrates. The article focuses on the role of cerebral CYP isoforms in the metabolism of neurotransmitters, neurosteroids, and cholesterol, and their possible involvement in animal behavior, as well as in stress, depression, schizophrenia, cognitive processes, learning, and memory. CYP-mediated alternative pathways of dopamine and serotonin synthesis may have a significant role in the local production of these neurotransmitters in the brain regions where the disturbances of these neurotransmitter systems are observed in depression and schizophrenia. The local alternative synthesis of neurotransmitters may be of great importance in the brain, since dopamine and serotonin do not pass the blood–brain barrier and cannot be supplied from the periphery. In vitro studies indicate that human CYP2D6 catalyzing dopamine and serotonin synthesis is more efficient in these reactions than the rat CYP2D isoforms. It suggests that these alternative pathways may have much greater significance in the human brain but confirmation of these assumptions requires further studies.

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Introduction

Cytochrome P450 (CYP) is a large family of monooxygenases with hemoprotein structure. As a part of a mixed function oxidase system, it cooperates with cytochrome P450 reductase in the oxidation of many endogenous substrates and xenobiotics in the body (Omura and Sato 1964). Eighteen families and 57 cytochrome subfamilies were distinguished in vertebrates based on the amino acid sequence similarity (Nelson 2011). The first three families CYP1-3 catalyze steroid metabolism and are the main enzymes that metabolize drugs and other xenobiotics in the body (Waxman 1988). Other families are mainly involved in the metabolism of endogenous substrates. Transmembrane proteins of cytochrome P450 are present in almost all tissues and their highest level is detected in the liver. The role of cytochrome P450 in the liver has been relatively well studied. It is a key enzyme in the synthesis of steroid hormones, drug metabolism, and detoxification of xenobiotics that facilitate their excretion from the body. Since the seventies, when the cytochrome protein was detected in the brain (Sasame et al. 1977), research has been conducted to find out the importance of the enzyme for the physiology and pharmacology of this most complex human organ coordinating the whole body in the physical and mental sphere. In general, the brain has the same enzymes as the liver, but a number of differences between organs have been identified. It was estimated that CYP concentration in the brain is 100 times lower than in the liver, generally, higher in neurons than in glial cells (Warner et al. 1988). Some CYP isoforms are found in certain brain cell types in concentrations higher than in the liver (CYP2D4 and CYP2B1) or are localized only in the brain (rat CYP2D18). Relatively high CYP concentration occurs in the vessels of the blood-brain barrier and in periventricular organs (no barrier) as a natural protection of the brain. The cerebral CYP isoforms show a wider cell localization than

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hepatic enzymes; they occur not only in the endoplasmic reticulum but also in the mitochondrial and nuclear membranes and are heterogeneously distributed in specific regions of the brain. The cerebral CYPs may create microenviroments of different drugs, endogenous substrates, and its metabolites concentrations, which cannot be monitored in the blood (Miksys and Tyndale 2004). It seems that the enzyme adapts in this way to the needs of histologically and functionally differentiated brain tissue. Furthermore, CYP isoforms in the liver and brain (brain regions) have differential induction profile, for example ethanol increases CYP2B1 expression only in the liver, while nicotine elevates CYP2B1 expression peculiarly in the brain. The study of Naud et al. (2016) showed that in the rat chronic renal failure-produced hyperparathyroidism, brain protein level and activity of CYP1A, CYP2C11, and CYP3A were downregulated, but their mRNA level remained unchanged. Similar effects were observed in the liver, but in this organ the mechanism of CYP downregulation was different, since it involved simultaneous decreases in mRNA levels (Michaud et al. 2006). Individual differences in the level of CYP expression in the brain may contribute to diverse responses to centrally acting drugs (e.g. psychotropics) and neurotoxins.

Regulation of the CYP in the brain occurs in a different way than in the liver. The unique response to regulatory factors is species specific and varies depending on the enzyme, brain structure and cell type (neurons and astrocytes). It seems that this may be due to the different distribution of nuclear receptors involved in the regulation of CYP expression in both organs. It was observed that the expression of receptors CAR and PXR is higher in the liver, while receptors PPARβ/δ and AhR dominate in the brain (Petersen et al. 2000; Nishimura et al. 2004). In addition, various splicing variants of nuclear receptors are detected in both organs. Like the CYP isoforms, nuclear receptors are located unevenly in different brain regions and cell types (thoroughly discussed in the review by Miksys and Tyndale 2013). A different response to regulatory factors may also result from the properties of the mutations of CYP genes. In the brain, genetic variants of the enzyme created by alternative mRNA splicing (CYP2D1, 2D7) were detected (Turman et al. 2006). The same CYP subfamilies in the liver and brain may differ in the proportion of the expression of individual isoenzymes, which in turn differ in their degree of affinity for common substrates and metabolic reactions. For example, the CYP2D subfamily of the rat is mainly represented by CYP2D1 and CYP2D2 in the liver while CYP2D4 is the most expressed in the brain. The specific regulation of cerebral CYP has been extensively discussed in previous reviews (Toselli et al. 2016; McMillan and Tyndale 2018).

The occurrence and distribution of CYP isoforms (expression and activity) belonging to CYP1-3 families in different regions and cell fractions of the human brain as well as endogenous and exogenous substrates of these CYP isoforms were comprehensively presented in the review article by Toselli et al. (2016). The associations of particular brain CYP isoforms with neurological diseases, such as epilepsy (Ghosh et al. 2017; Asai et al. 2018; Runtz et al. 2018), neurodegenerative (Navarro-Mabarak et al. 2018) and neurovascular (Ghosh et al. 2016; Davis et al. 2017) diseases, were recently competently discussed. This article mainly concentrates on possible implication of brain CYPs in mental illnesses and accompanying cognitive/memory disturbances.

Brain cytochrome P450 and depression

Depression is the most widespread psychiatric disease in the contemporary human population in the world. The incidence of depression increases despite the development of pharmacotherapy, and generates large social costs. Depression most often attacks citizens of highly developed countries and its main cause is the growing stress and rush of life. The most common symptoms of depression include feelings of sadness, anxiety, tiredness, and distress. It is currently assumed that this brain disorder is caused by a combination of various genetic, environmental, and neurobiological factors. The monoamine-deficiency hypothesis proposed by Schildkraut (1965) is the main and the oldest theory of depression. Today, it is believed that the disturbances in neurotransmission involving the catecholamine neurotransmitter norepineprine and the indoleamine neurotransmitter serotonin in the brain limbic system (prefrontal cortex, hippocampus) play a significant role in pathophysiology of depression. On the other hand, the serotonin hypothesis of depression proposed in the 1960s postulated that the deficit in brain serotonin reversed by antidepressants was the primary origin of the disease (Coppen 1967). The post-mortem studies and research in the field of genetics, neurochemistry, neuroimaging and neuropharmacology suggest that functional insufficiency in serotonin neurotransmission affects negatively emotions and may participate in the pathophysiology of depression (Belmaker and Agam 2008).

Serotonin is a multitask neurotransmitter and, depending on the structure of the brain, performs important physiological and behavioral functions.

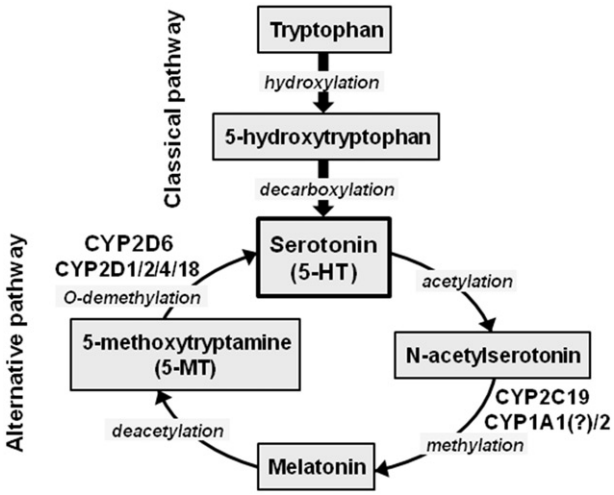

Figure 1. Serotonin synthesis in the brain *via* classical and alternative CYP2D-catalyzed pathway.

Serotonergic pathways originate from the clusters of neurons in the raphe nuclei of the brainstem and project to almost all areas of the central nervous system. From the dorsal and medial raphe nuclei, serotonergic neurons reach the forebrain structures. In this region, in specific brain structures, serotonin released from nerve endings fulfills many significant functions, e.g. it is a mediator of motor functions (basal ganglia), and participates in the control of appetite, circadian rhythm, thermoregulation (hypothalamus), sleep regulation (thalamus), learning, memory processes and stress (hippocampus), and mood and sleep control (brain cortex) (Di Giovanni et al. 2008).

Serotonin in the brain is mainly synthesized from tryptophan, an exogenous substrate obtained from food that easily penetrates the blood–brain barrier, *via* hydroxylation to L-5-hydroxytryptophan and further decarboxylation (Figure 1). The activity of tryptophan hydroxylase 2 is the limiting step in the synthesis of serotonin (Stahl 2013). Recent studies have shown that the classical pathway for the synthesis of serotonin from tryptophan is not the only way to produce serotonin in the brain. Using *CYP2D6*-transgenic mice and recombinant enzymes Yu et al. (2003) have demonstrated that the human CYP2D6 isoform was capable of catalyzing the *O*-demethylation of 5-methoxytryptamine (5-MT) to serotonin in the liver. The serotonin regeneration reaction from 5-MT closes the cycle of melatonin–serotonin biotransformations (Yu et al. 2003). These studies initiated the work on an alternative pathway for the synthesis of serotonin *via* CYP2D to demonstrate its functional role in the brain. The endogenous trace amine 5-MT is mainly produced from gut-derived melatonin (*via* deacetylation) in the liver and can penetrate the blood–brain barrier. Melatonin and the enzyme catalyzing its biosynthesis arylalkylamine N-acetyltransferase are detected in different brain areas. However, in the brain, the production of melatonin and 5-MT takes place mainly in the pineal gland. Both indoleamines are released to the circulation or to the third ventricle of the brain. 5-MT is also detected in other brain structures, e.g. in the raphe nuclei of the brain stem containing cell bodies of serotonergic neurons (reviewed in Haduch et al. 2016). The *in vitro* study showed a good correlation between the distribution of CYP2D activity and the regional formation of serotonin from 5-MT (Haduch et al. 2013b). The above data suggest that CYP2D may catalyze the *O*-demethylation of 5-methoxytryptamine to serotonin in the brain *in vivo*. The alternative pathway of serotonin synthesis closing the cycle of melatonin-serotonin biotransformations may prevent the deprivation of biological activity of indolethylamines by monoamine oxidase in the brain.

In vitro study with brain microsomes provided the first evidence for the hypothesis that the *O*-demethylation of 5-methoxytryptamine to serotonin may proceed in the brain (Haduch et al. 2013b). This reaction occurred in the microsomes from various rat brain regions, like limbic structures (e.g. the frontal cortex, the hippocampus) and the cerebellum, containing the highest amount of CYP2D. The *O*-demethylation of 5-methoxytryptamine was inhibited by specific CYP2D inhibitors, indicating that it is catalyzed by this enzyme. Screening studies on recombinant major CYP isoforms confirmed that isoforms of CYP2D1/2 and the main brain CYP2D isoform CYP2D4/18, are the main CYP enzymes responsible for biotransformation of 5-MT to serotonin in the rat. Interestingly, it was observed that human CYP2D6 is more efficient at catalyzing 5-MT *O*-demethylation to serotonin than the rat CYP2D isoforms. Therefore, a stronger positive effect of CYP2D6 in the human brain on the level of serotonin and indirectly on the level of melatonin seems to be very likely. Both indoleamines are of antidepressant significance, which underlines the importance of CYP2D for normal brain function.

It is difficult to practically show the functioning of an alternative pathway of serotonin synthesis in the human brain *in vivo,* since it is difficult to distinguish serotonin formed by CYP2D pathway from serotonin synthesized by the classical pathway (Figure 1). Serotonin formed by CYP2D is hidden in the whole pool of the neurotransmitter which is predominantly supplied by the classic pathway *via* tryptophan hydroxylase and stored in neuronal vesicles in nerve endings. In animal study carried out after 5-MT injection into the

raphe nuclei of rats with inhibited the classic pathway of serotonin synthesis, significant increases in the total tissue concentration of serotonin were observed in the hippocampus, cortex, and a similar tendency was noticed in the hypothalamus and frontal cortex (Haduch et al. 2015). Quinine, a specific CYP2D inhibitor, significantly decreased tissue levels of serotonin in the hippocampus and cortex, and, to a lesser extent, diminished it in the hypothalamus and frontal cortex. On the other hand, 5-MT given intrastructurally through a microdialysis probe markedly elevated extracellular serotonin concentration in the frontal cortex. Quinine given jointly with 5-MT prevented the 5-MT-induced increase in cortical extracellular serotonin in naïve rats (Haduch et al. 2015). Besides, melatonin, an indirect substrate for the serotonin synthesis by CYP2D-mediated 5-MT *O*-demethylation, given intraperitoneally increased serotonin tissue level in the hippocampus, hypothalamus, cerebellum, and in other structures, which was also markedly decreased by quinine (Haduch et al. 2016). Another study with the model of *CYP2D6*-transgenic mice showed a higher tissue level of serotonin and its metabolite 5-HIAA in the cerebellum, hippocampus, and other brain regions of mice having human *CYP2D6* gene than in wild type mice (Cheng et al. 2013). These *CYP2D6*-transgenic mice showed less anxiety in behavioral tests. Thus, the results of the studies conducted on laboratory animals provide reliable evidence indicating that in rodents serotonin may be synthesized *via* the alternative CYP2D-mediated pathway from 5-methoxytryptamine. It is very likely that the same pathway functions in the human brain *in vivo* and to some extent may help in restoring the proper level of serotonin reduced during depression, especially considering that human CYP2D6 isoform was more effective in catalyzing 5-MT *O*-demethylation to serotonin than rat CYP2D isoforms (Haduch et al. 2013a,b). It is likely that human brain CYP2D6 has a positive effect on maintaining the normal level of physiologically active indoleamines like serotonin and melatonin (Haduch et al. 2015). Its role can grow under the conditions of an impairment of the classical pathway of serotonin synthesis *via* tryptophan hydroxylase and/or when *CYP2D6* gene is duplicated or multiplied or when cerebral CYP2D is activated in different brain structures by inducers such as alcohol, nicotine, psychotropics – nefazodone, fluoxetine, thioridazine, and clozapine. (Miksys et al. 2002; Mann et al. 2008; Haduch et al. 2011; Yue et al. 2008; Miller et al. 2014).

The premises from *in vivo* studies in humans suggest the functional significance of the brain CYP2D6 in depression (Ingelman-Sundberg et al. 2014). The poor metabolizer (PM) phenotype, representing genotype characterized by the *CYP2D6* genetic defect increases the risk of depression. A relatively higher frequency of PM phenotype was observed in the depressed patients compared to healthy people (Háber et al. 2013; Cacabelos et al. 2016). Besides, in association studies, the relationship between the *CYP2D6* genotypes and the specific personality traits was demonstrated. Individuals with CYP2D6 genetic defect and CYP2D6 poor metabolizer phenotype (PM) showed greater anxiety, impulsivity and social maladjustment compared to extensive metabolizers (EM) (Bertilsson et al. 1989; Llerena et al. 1993; Gonzáles et al. 2008; Peñas-Lledó and Llerena 2014). Results of this study suggest that polymorphic brain CYP2D6 plays an important role in endogenous metabolism of the brain and, therefore, can affect human behavior and vulnerability to mental diseases. On the other hand, it is suggested that CYP2D6 ultrarapid metabolizer (UM) phenotype is conducive to an increased risk of suicide (Zackrisson et al. 2010; Stingl et al. 2012a), which is also elevated in patients with a high CYP2D6-CYP2C19 metabolic capacity (Peñas-Lledó et al. 2015).

Beside CYP2D6, the polymorphic CYP2C19 isoform plays an important role in the metabolism of many endogenous substrates and may also contribute to pathophysiology of depression. CYP2C19 is detected only in human fetal brain and its expression disappears after birth, suggesting the involvement of the enzyme in brain development (Persson et al. 2014). Thus, the activity of the fetal brain polymorphic CYP2C19 seems to have a significant impact on the risk of appearance of depressive mood in adulthood. Sim et al. (2010) observed an association between poor metabolizers of CYP2C19 phenotype, lacking active enzyme (homozygous with two defective variants allele *CYP2C19*2*2*) with lower level of depressive symptoms, in comparison to extensive metabolizers (*CYP2C19*1*1*) in Swedish older adult (45–98 years old) subjects. Studies with a transgenic *CYP2C19* mouse model (2C19TG) confirm the importance of polymorphic brain CYP2C19 in depression. Adult 2C19TG mice showed increased anxiety in behavioral tests and decreased hippocampal volume in comparison to wild-type adult mice (Persson et al. 2014). The reduction of hippocampal volume is often observed in neuropsychiatric diseases, like depression or schizophrenia. Further studies demonstrated high stress sensitivity and a strong anxiety-like behavior in transgenic 2C19TG mice in the forced swim test and unsettled hippocampal serotonin and BDNF homeostasis (Jukić et al. 2017). Besides, in human study the same authors have observed that the lack of CYP2C19 was

associated with increased bilateral hippocampal volume, while raised CYP2C19 expression was associated with depressive phenotype in African-American subjects (Jukić et al. 2017). The relationship between the CYP2C19 phenotype and depression suggests that CYP2C19 in the fetal brain plays an important role in maintaining metabolic homeostasis and affects personality traits and behavior of adult humans. *In vitro* studies suggest that CYP2C19 is involved in the metabolism of polyunsaturated fatty acids, such as arachidonic acid, eicosapentaenoic acid, and psychoactive steroid hormones, such as estradiol, estron, progesterone, and testosterone, which may affect embryonic development and also adolescent brain maturation (Persson et al. 2014). Besides, a possible contribution of CYP2C19 to the biotransformation of serotonin has been suggested (Fradette et al. 2004), but the endogenous brain substrates of this CYP isoform involved in the brain development and depressive phenotype require further detailed identification.

Another theory points to deficient synthesis of neurosteroids which have been indicated as factors conducive to the development of depression (Belmaker and Agam 2008; Zorumski et al. 2013). Neurosteroids produced in the brain act as effective neuromodulators controlling the proper functioning of the brain, and imbalance in their metabolism may be the cause of mental illness and activation of the immune system. The relationship between the level of neurosteroids and the occurrence of the disease entity was confirmed, among others, in the case of depression, dementia and epilepsy (Stoffel-Wagner 2001). Neurosteroids are synthesized from cholesterol in the mitochondrial membranes of neurons and glial cells. These neuroactive agents affect the function of various signaling pathways, among others, receptors for γ-aminobutyric acid (GABA) and glutamate, the important inhibitory and excitatory neurotransmitters in the central nervous system (Zorumski et al. 2013). Many CYP isoforms with detectable expression in the brain are involved in the metabolic pathways of steroids and maintain its homeostasis in the central nervous system. Brain CYP51 isoform plays a crucial role in local biosynthesis of cholesterol. CYP46 isoform mediates the elimination of cholesterol, and its expression is 100 times higher in the brain than in the liver, which indicates the importance of this process in brain neuroprotection. Other brain CYPs catalyze the metabolic pathways of cholesterol leading to the synthesis of neurosteroids, many of which have neuroprotective and antidepressant effects, like allopregnanolone and dehydroepiandrostenedione (DHEA) (Schüle et al. 2014; Samardzic et al. 2017). The initial step of neurosteroidogenesis involves the biotransformation of cholesterol to pregnenolone catalyzed in mitochondria by CYP11A followed by progesterone formation (Figure 2). CYP17A1 acts as a neurosteroid 17-hydroxylase allowing for further synthesis of DHEA, testosterone and estradiol (*via* conversion of testosterone by CYP19A1 aromatase) from progestagens (Liu et al. 2004). In postmortem study, a significant decrease in CYP17A1 mRNA level was observed in the prefrontal cortex, anterior cingulate cortex and dorsolateral prefrontal cortex of patients with major depressive disorder, which may indicate the presence of a disturbance in the endogenous synthesis of DHEA in mood disorders (Qi et al. 2018). Studies with recombinant isoforms of CYP2D subfamily showed that human CYP2D6 and rat CYP2D1, 2D4 possess steroid 21-hydroxylase activity and oxidize neuroprotective neurosteroids including progesterone, pregnenolone, and allopregnanolone. 21-Hydroxylation of these neurosteroids has been demonstrated in rat brain microsomes *in vitro* (Hiroi et al. 2001).

In vivo studies showed that the influence of psychotropics on brain CYP2D activity after chronic treatment was different than in the liver and was structure dependent (Haduch et al. 2011). Like in the liver, fluoxetine decreased the CYP2D activity in the striatum and the nucleus accumbens, but increased the enzyme activity in the cerebellum. Interestingly, clinical studies showed a significantly decreased level of allopregnanolone in plasma and cerebrospinal fluid in individuals with depression. The lower level of this neurosteroid was normalized by treatment with fluoxetine, sertraline and tricyclic antidepressants, which are known CYP2D inhibitors (Romeo et al. 1998; Uzunova et al. 1998; Ströhle et al. 1999, 2000; Rasmusson et al. 2006). It seems that the inhibition of CYP2D activity by antidepressants may affect the metabolism of neurosteroids *in vivo*, leading to an increase in their concentration in the brain, and thus to the positive modification of the pharmacological effect of antidepressants (Uzunov et al. 1996; Pinna et al. 2006). On the other hand, nefazodone administered chronically diminished the enzyme activity in the liver, but increased CYP2D activity in the brain stem (Haduch et al. 2011). The significant positive effect of nefazodone on CYP2D activity in the brain stem seems to be beneficial for antidepressant therapy, since the brain stem contains both serotonergic neurons of the raphe nuclei and dopaminergic neurons of the ventral tegmental area (VTA). It is possible that, by increasing CYP2D activity in the brain stem, nefazodone may accelerate serotonin regeneration from 5-methoxytryptamine and tyramine

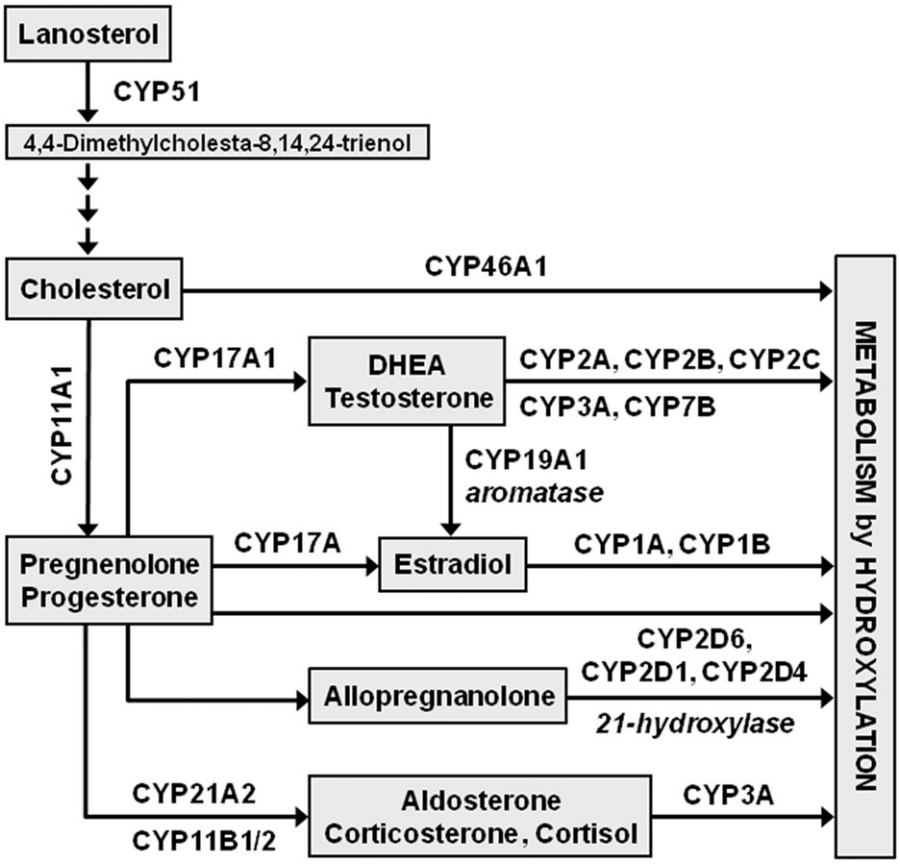

Figure 2. Cytochrome P450-catalyzed metabolism of cholesterol and neurosteroids in the brain.

hydroxylation to dopamine (discussed in the next chapter), which may affect the faster appearance of the antidepressant effect of nefazodone in comparison with other antidepressants (Haduch et al. 2011).

Brain cytochrome P450 and stress

Clinical observations show that a long-lasting stress can lead to the development of depression. The hypothalamic–pituitary–adrenal (HPA) axis called the stress axis is one of the two main biological systems involved in the stress response alongside the sympathetic system. Stress is discerned by the brain cortex and the amygdala and transmitted to the hypothalamus. In response to stress, hypothalamus releases corticotropin-releasing hormone (CRH), which induces the anterior pituitary gland to the secretion of corticotropin into the blood. In turn, corticotropin stimulates the adrenal cortex to secrete cortisol. This glucocorticoid hormone suppresses the production of CRH in the hypothalamus and corticotropin in the pituitary to keep homeostasis through feedback inhibition (Belmaker and Agam 2008). Stress can decrease the expression of the neurotrophic factor BDNF (which preserves the viability of neurons) and reduce the serotonin level in the brain. As concerns catecholamines, acute stress can increase noradrenaline and dopamine levels, but chronic stress decreases the level of these neurotransmitters. The deficiency of BDNF and changes in the levels of monoamine neurotransmitters may cause atrophy and apoptosis of neurons in different brain structures, especially in the hippocampus. Hippocampal neurons suppress the HPA axis in normal condition, so atrophy of these neurons caused by stress can lead to overactivity of the HPA axis (Willner 2017). There is a lot of evidence that the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis observed under strong or long-lasting stress is involved in the pathology of depression. Patients suffering from depression may display the elevated concentration of plasma cortisol and cerebrospinal fluid CRH, the increased size of the anterior pituitary and adrenal cortex, and the diminished size of the hippocampus and amygdala associated with atrophy of neurons (Belmaker and Agam 2008).

Studies on animal models of psychological stress, like repeated restraint stress (RS), early-life maternal deprivation (MD), or chronic mild stress (CMS) indicate that psychological stress can modify expression of

hepatic CYP isoforms in a stress-specific way (Konstandi 2013; Daskalopoulos et al. 2012; Kot et al. 2017). However, there is little research on the effect of stress on CYP enzymes in the brain. One study showed that stress (cold-hypoxic restraint) significantly induced the CYP1A1 and CYP2B1/2 activity in several brain structures – in the hippocampus, the cerebral cortex, the cerebellum, and the rest of rat brain (Chowdhuri et al. 2002). The authors investigated the anti-stress effect of the bacosides of *Bacopa monnieri* a plant known for its beneficial effects on the nervous system (ayurvedic medicine). Mixture of bacosides administered alone (p.o.) caused a significant increase in the activity of CYP1A1 and CYP2B1/2, but 7-d pretreatment with bacosides before stress exposure prevented the increases in the activities of two tested brain CYP isoforms in all brain structures studied. These two CYP subfamilies take part in the metabolism of neurosteroids (Ryan and Levin 1990; Arlotto et al. 1991; Gokhale et al. 1997; Badawi et al. 2001).

Our recent study on the brain and liver CYP2D in chronic mild stress (CMS), the animal model of depression, showed that CMS significantly increased the brain CYP2D activity in the hippocampus without affecting the hepatic enzyme (Haduch et al. 2018). The elevated CYP2D activity in the hippocampus may be a protective response to CMS. Chronic administration of escitalopram and venlafaxine had a different effect on the CYP2D activity in the brain compared with the liver. These antidepressants significantly elevated the enzyme activity in the frontal cortex, hypothalamus and cerebellum in stressed animals without causing changes in the brain CYP2D activity in non-stressed rats. It seems that CMS triggers the stimulatory effect of escitalopram and venlafaxine on the CYP2D activity, normalizing the synthesis of some endogenous substances playing an important role in brain physiology, like serotonin or dopamine (Haduch et al. 2018).

Brain cytochrome P450 and schizophrenia

Schizophrenia is a complex neuropsychiatric disease with a mixture of characteristic positive (delusions and hallucinations) and negative (apathy, anhedonia, and cognitive blunting) symptoms. Various genetic and environmental factors are involved in the etiology of this disorder, which affects 0.5% of the world's population (Ebdrup et al. 2011).

Different neurotransmitter systems have been discussed to be engaged in the pathophysiology of schizophrenia but the main hypothesis of this disease is based on dopamine. Dopaminergic system in the brain consists of several pathways. The most important among them include the mesolimbic dopaminergic pathway, mesocortical dopaminergic pathway, nigrostriatal dopaminergic pathway, and tuberoinfundibular dopaminergic pathway (Stahl 2013). The mesolimbic pathway projects from the dopaminergic neurons in the ventral tegmental area (VTA) of the brain stem to the nucleus accumbens in the ventral striatum in the limbic system. The mesolimbic pathway is involved in the regulation of emotional behaviors and hyperactivity of this pathway is believed to account for positive symptoms of schizophrenia (delusions, hallucinations). Currently used antipsychotic drugs capable of alleviating positive psychotic symptoms are blockers of dopamine D_2 receptors. The mesocortical dopamine pathway also begins in the ventral tegmental area, but projecting to different areas of the prefrontal cortex and is engaged in the regulation of cognition, executive functions, emotions and affect. It is believed that the mesocortical pathway mediates negative, cognitive, and affective symptoms of schizophrenia which may arise from hypoactivity in this pathway. It seems that the opposite changes in dopamine activity in different dopaminergic pathways cause simultaneously various symptoms of schizophrenia. In turn, the nigrostriatal dopamine pathway beginning in the brainstem substantia nigra and ending in the basal ganglia (the striatum) controls motor behaviors. The lowered level of dopamine in this extrapiramidal pathway causes movement disorders, like Parkinson's disease or the side-effects induced by typical neuroleptics and to a lesser extent by atypical ones, which results from their different inhibitory potency on dopaminergic and serotonergic receptors (Meltzer 2013).

The main dopamine pool in the brain derives from the synthesis via classic pathway from phenylalanine. Phenylalanine hydroxylase transforms this substrate into tyrosine, which then is converted *via* tyrosine hydroxylase to dihydroxyphenylalanine (Figure 3). At the final stage of synthesis dihydroxyphenylalanine is metabolized by aromatic amino acid decarboxylase to dopamine. Brain CYP2D, that catalyzes the alternative pathway of serotonin synthesis from 5-methoxytryptamine, can also catalyze the alternative dopamine formation from tyramine. Tyramine is a trace endogenous amine formed in the brain from phenylethylamine (*via* hydroxylation) or tyrosine (*via* decarboxylation). Tyramine from food does not cross the blood–brain barrier (Berry 2004). The hydroxylation of tyramine to dopamine *via* CYP2D was first demonstrated for rat liver microsomes and human cDNA-expressed CYP2D6 (Hiroi et al. 1998). In further studies, the hydroxylation of

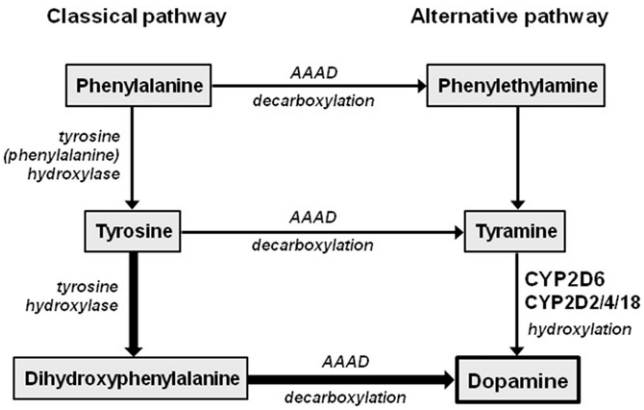

Figure 3. Dopamine synthesis in the brain *via* classical and alternative CYP2D-catalyzed pathway. AAAD: aromatic amino acid decarboxylase.

tyramine to dopamine was demonstrated in rat brain microsomes, what suggested that the alternative pathway of dopamine synthesis might occur in the brain (Bromek et al. 2010). This reaction was decreased by quinine, a CYP2D inhibitor and anti-CYP2D4 antibodies, indicating that CYP2D plays a significant role in dopamine synthesis. The rat CYP2D isoforms capable of forming dopamine from tyramine (CYP2D2, 2D4, and 2D18) were less efficient than human CYP2D6 in this reaction. It suggests that the alternative pathway of dopamine synthesis via CYP2D can be more important in the human brain than in the rodents' brain. In the experiments carried out on reserpinized rats with a blockade of the classical pathway of dopamine synthesis from tyrosine, tissue and extracellular dopamine levels were studied *in vivo* (Bromek et al. 2011). The study demonstrated that the CYP2D inhibitor quinine given intraperitoneally significantly decreased the total tissue level of dopamine in the striatum and nucleus accumbens, and tended to do so in the substantia nigra and frontal cortex. On the other hand, an increase in extracellular dopamine level was observed after tyramine given intrastructurally into the striatum (brain microdialysis), and was significantly lower after joint administration of tyramine and quinine (Bromek et al. 2011). The above results provided a good evidence for CYP2D-mediated dopamine formation from tyramine in the brain *in vivo*. Although this pathway is difficult to observe under physiological condition in rats, it may be more efficient in the human brain, as indicated by an *in vitro* study with cDNA-expressed rat and human CYP2Ds (Bromek et al. 2010). The significance of this reaction in the human brain may increase under specific conditions, such as the pathological deficiency (following neurodegeneration or mutation) of the main enzymes synthesizing dopamine, i.e. tyrosine hydroxylase or aromatic amino acid decarboxylase (Verbeek et al. 2007; Wassenberg et al. 2010; Willemsen et al. 2010) and/or an increased CYP2D6 activity due to *CYP2D6* gene multiplication or the enzyme induction (as mentioned earlier).

In vitro study of rat brain CYP2D activity, estimated as the rate of bufuralol 1′-hydroxylation in different brain structures related to the pathology and treatment of schizophrenia, showed a relatively high level of CYP2D activity in the substantia nigra and striatum (nigrostriatal pathway), nucleus accumbens and frontal cortex (mesolimbic pathway), brain stem (the beginning of the mesolimbic and mesocortical dopaminergic pathways), and cerebellum (Bromek et al. 2010). Therefore, it seems that CYP2D-mediated alternative biosynthesis of dopamine in the brain may have some implications for different psychiatric and neurological illnesses, like schizophrenia, Parkinson's disease or addiction. It seems that the inhibition of cerebral CYP2D activity does not significantly affect the overall dopamine pool in the brain, because it is maintained by the dominant classical pathway of the neurotransmitter synthesis from tyrosine. However, stimulation of dopamine synthesis *via* an alternative pathway through CYP2D6 induction may have various beneficial effects depending on the region of the brain in which the enzyme activity could be elevated. An increase in the CYP2D activity in the mesocortical dopaminergic pathway, in which dopamine deficit is observed in schizophrenia, could alleviate the negative symptoms of the disease and improve the cognitive and memory processes by increasing the production of dopamine *via* an alternative pathway. During treatment of schizophrenia with neuroleptics that block D_2 receptors, CYP2D catalyzing dopamine synthesis in the nigrostriatal dopaminergic pathway could mitigate the extrapyramidal side-effects of these drugs. However, the increased dopamine synthesis *via* CYP2D-mediated alternative pathway in the mesolimbic

dopaminergic pathway would be disadvantageous. But probably it may not matter too much during neuroleptic treatment, because of D_2 receptor blockade.

Studies of the influence of psychotropic drugs on CYP2D in the brain demonstrated that their effect was different than in the liver and depended on the cerebral structure (Haduch et al. 2011). Chronic administration of thioridazine, a typical neuroleptic and known inhibitor of the hepatic CYP2D, caused a significant increase in the CYP2D activity in the striatum and the cerebellum in the rat. It is conceivable that the increased production of dopamine by CYP2D in the nigrostriatal system could relieve the extrapyramidal side-effects of thioridazine, since this neuroleptic causes minor extrapyramidal side-effects in patients compared to other typical antipsychotics (Thanacoody 2011). Clozapine, an atypical neuroleptic administered chronically, significantly increased CYP2D activity in the brainstem (in particular in the VTA) and showed a similar tendency in the cerebellum in the rat (Hedlund et al. 1996; Haduch et al. 2011). The observed beneficial effect of clozapine on cognitive processes and negative symptoms of schizophrenia in patients (Khan and Zaidi 2017) may result not only from the receptor profile of the drug, but also in part from the intensification of the alternative pathway of dopamine synthesis on the mesocortical dopaminergic pathway. It seems that the induction of CYP2D in the brain by neuroleptics may become an additional component of their pharmacological action (Haduch et al. 2011). Interestingly, schizophrenic patients are more likely to abuse nicotine than healthy adults (Dalack et al. 1999; Hahn et al. 2013). It could be explained as an attempt to boost the function of defective mesocortical dopamine pathway involved in motivation, pleasure and reward (Stahl 2013; Potvin et al. 2016). Considering that nicotine is a known inducer of cerebral CYP2D activity, it is possible that it may trigger alternative neurotransmitter synthesis pathway in the brain, in defense against negative symptoms and cognitive deficits of schizophrenia.

Brain cytochrome P450 and cognitive, learning, and memory processes

Current studies looking for new functions of cytochrome P450 in the brain revealed the association of the cerebral CYP with cognitive processes, memory and learning. As mentioned before, it is known that several CYP isoforms play an important role in the metabolism of cholesterol in the brain and in the synthesis of neurosteroids arising therefrom. The level of cholesterol in the brain depends on its local *de novo* synthesis in glial cells, because cholesterol cannot freely penetrate across the blood–brain barrier from the periphery. Brain CYPs play a pivotal role in cholesterol homeostasis (Zhang and Liu 2015). CYP51 is the most important enzyme mediating the synthesis of cholesterol in the brain, while CYP46A1 (expressed only in neurons) allows for its elimination by hydroxylation to 24(R) and 24(S)-hydroxycholesterol (Figure 2). Research data indicate that the disturbances in cholesterol homeostasis are associated with memory deficits and the risk of developing neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and others. In clinical studies, the increased 24-hydroxycholesterol and 27-hydroxycholesterol levels were observed in the cerebrospinal fluid of Alzheimer's disease (AD) patients. Higher levels of these metabolites in the cerebrospinal fluid suggest the elevated level of cholesterol in the brain, which was observed in a postmortem study in AD brains together with senile plaques and neurofibrillary tangle deposits (Wang et al. 2016). Moreover, it suggests that *CYP46 A1* polymorphisms affect the risk of developing this disease (Garcia et al. 2009; He et al. 2012; Jia et al. 2016). In the hippocampus of C57BL/6 mice, the expression of the *CYP46A1* gene encoding the cholesterol 24-hydroxylase was experimentally decreased which led to an increase in the cholesterol concentration in neurons. The excessive cholesterol caused apoptosis of hippocampal neurons and cognitive deficits. These effects were more pronounced in the transgenic mice APP23 model of Alzheimer's disease compared to normal mice (Djelti et al. 2015). In another study, female homozygous CYP46A1 transgenic mice with overexpression of cholesterol 24(S)-hydroxylase, demonstrated an improvement in spatial memory in the Morris water maze test as compared to the wild type mice. The authors suggest that the increased level of CYP46A1 has a positive influence on cognition and synaptic plasticity in old female mice (Maioli et al. 2013).

Cholesterol is also the starting substrate for the synthesis of steroid hormones. Androgens and estrogens are important modulators of neural function. They regulate synaptic and glial plasticity, hippocampal neurogenesis, and the response of cerebral tissue to neurodegeneration or injury. Steroid hormones are known of modulating behavior, learning, and memory (Melcangi et al. 2008). Androgens and estrogens in the brain come not only from the periphery, but are also produced locally in the brain *via* CYP isoforms, like CYP11A1, 17A1, and 19A1 (Figure 2). The expression of these steroidogenic enzymes has been established in several brain regions, also in the mesocorticolimbic system. The presence of CYP17A1 and CYP19A1 aromatase

was found in the VTA, nucleus accumbens and medial prefrontal cortex (Tobiansky et al. 2018b). The authors suggest that testosterone has significant effects on the mesocorticolimbic system and can play some role in motivated behaviors. The male testosterone-sensitive sexual behaviors are maintained in a significant percent of subjects after gonadectomy. These data indicate that the local synthesis of testosterone in the brain modulates the sexual behavior of males lacking a peripheral source of steroid hormones. It was shown that many male rats have detectable level of brain testosterone long time after gonadectomy in the VTA, nucleus accumbens, and medial prefrontal cortex, where the androgenic enzymes CYP17A1 and CYP19A1 expressions were detected (Murakami et al. 2006; Tobiansky et al. 2018a). A lot of studies indicate that estrogens and especially estradiol have a very positive effect on learning and memory processes (Colciago et al. 2015). CYP19 aromatase plays a crucial role in estrogen biosynthesis converting androgens to estrogens. This enzyme is expressed in both neurons and astrocytes. In ovariectomized mice, 17β-estradiol administered tonically *via* minipellets (s.c.) up-regulated the hippocampal expression of CYP19 and estrogen receptors, and improved spatial memory in mice in behavioral tests (Iivonen et al. 2006). Recent studies indicate that the steroidogenic CYPs' expression in the hippocampus significantly decreases with age, which is associated with a decrease in hippocampal estradiol level and spatial memory decline observed in the behavioral tests in the rat. The increased expression of interleukin 6 in the microglia of aged brain suppressed CYP synthesis, which directly inhibited estradiol production in hippocampal neurons contributing to the deficit of spatial memory performance (Chamniansawat and Sawatdiyaphanon 2018). Central intraventricular administration of a CYP7B product 7α-hydroxypregnenolone to cognitively impaired aged rats improved spatial memory retention (Yau et al. 2006). Other drug-metabolizing enzymes involved in the metabolism of neurosteroids comprise CYP1A, CYP2A, CYP2B, CYP2C, and CYP3A isoforms, which catalyze testosterone hydroxylation in specific positions (Ryan and Levin 1990; Arlotto et al. 1991; Gokhale et al. 1997; Badawi et al. 2001).

Recent studies also suggest that in addition to the CYP enzymes involved in neurosteroidogenesis, also drug-metabolizing enzymes expressed in the hippocampus and cerebellum may be involved in learning process in rodents (Gjota-Ergin et al. 2018; Zhang et al. 2018). In the hippocampus, the brain center of learning and memory, the expression of the three CYP isoenzymes CYP2E1, CYP2D1, and CYP7A1 was studied in the behavioral tests based on food reinforcement in the 12-arms maze (Gjota-Ergin et al. 2018). A positive correlation was found between the protein levels of these isoenzymes with cognitive performance at different stages of memory tasks training. In the good learner rats (compared to the poor learner animals), significantly higher CYP protein levels were observed at the early stage of training (CYP2E1), at the intermediate stage of training (CYP2D1) and after reaching the acquisition criterion (CYP7A1). The obtained results suggest that hippocampal expression of these CYPs is dependent on the stage of learning and animal cognitive status. It seems that the differential expression of some brain CYPs in the hippocampus may be related to individual learning skills.

For a long time, the cerebellum was attributed primarily the role in movement control. However, newer findings indicate that the cerebellum also plays a role in other functions. Studies using the functional brain imaging method showed the activity of the cerebellum related to language, attention and mental areas. It has been shown that the cerebellum has connections with non-motor cortical and subcortical regions associated with emotional processing, like the limbic system (Caligiore et al. 2017). Additionally, the cerebellum is connected with brain stem nuclei, which provide the limbic system and other brain areas with serotonin, norepinephrine and dopamine. In patients with cerebellar cognitive-emotional syndrome (Schmahmann syndrome) associated with cerebellar injury, deficits in executive functions, spatial cognition and language, changes in personality, disturbed behavior, mood, and emotional blunting were found (Schmahmann 2004). Moreover, the cerebellar lesions in patients were associated with a greater risk of depression, with emotional and behavioral problems. The contribution of the cerebellum to the pathophysiology of depression and schizophrenia has also been suggested (Andreasen and Pierson 2008; Wolf et al. 2009; Schutter 2016; Caligiore et al. 2017). Interestingly, the CYP2D enzyme, which appears to have a significant contribution to endogenous brain metabolism, exhibits the high expression and activity in the cerebellum (Tyndale et al. 1999; Miksys et al. 2000; Bromek et al. 2010; Wang et al. 2014). Zhang et al. (2018) demonstrated that the inhibition of the CYP2D activity in the cerebellum with its specific inhibitor quinine administered into the brain negatively affected the spatial learning and exploratory behavior of mice in the Morris water maze tests. Furthermore, the results of elevated plus maze experiments indicate that the decreased CYP2D activity in the cerebellum

increases anxiety-related behavior in mice. This is another *in vivo* evidence of the functional role of cerebral CYP2D in the metabolism of neuroactive endogenous substrates and behavior.

Besides, the functional brain imaging studies indicate a possibility of predicting CYP2D6 phenotype and provide evidence that basic cognitive processes related to attention and alertness may be impacted by the CYP2D6 genetic polymorphism (Stingl et al. 2012a, 2012b; Napolitano et al. 2017).

Conclusions

The presented data from different scientific laboratories and clinics indicate an important role of the brain cytochrome P450 in the local metabolism of endogenous substrates necessary for the proper functioning of the brain and maintaining its homeostasis. General features of the brain cytochrome P450 have been defined and include: the enzyme regulation different than in the liver, heterogeneous distribution in different brain regions/cell types, different susceptibility to inhibition, and induction dependent on the brain structure/cell type, the expression of CYP isoforms specific for the brain. These features suggest that brain CYP, although it has low expression compared with the liver, can participate in many metabolic pathways that function in different brain regions specializing in the management of specific processes.

In vitro studies with the use of recombinant CYPs and brain microsomes have demonstrated the ability of several CYP isoforms to catalyze the metabolism of many important endogenous brain substrates (e.g. monoaminergic neurotransmitters, neurosteroids, cholesterol, fatty acids, arachidonic acid), which is often disturbed during mental and neurodegenerative diseases. These catalytic properties of CYPs are correlated with the changes in CYPs' expression/activity observed in the brain of the laboratory animals *ex vivo* and in the human brain (*postmortem* studies) in physiological or in various pathological conditions, and with polymorphisms of the genes encoding CYP isoforms. *In vivo* studies on laboratory animals (brain microdialysis) and in humans (neuroimaging study) carried out in recent years confirm the involvement of CYP in the brain metabolism of endogenous neuroactive substrates and drugs. Many studies suggest the links of cerebral CYP and their endogenous substrates with neurodegenerative diseases, such as Parkinson's disease or Alzheimer's disease. The brain CYPs may be also involved in stress and mental illnesses such as depression or schizophrenia and psychopharmacotherapy. The most connections with these diseases have been shown for the CYP isoforms that simultaneously metabolize psychotropic drugs used in the therapy of these diseases and endogenous substrates in the brain. These brain CYPs modify the drug action at the site of pharmacological action in the brain and reveal a new component of the therapeutic action of the psychotropic drugs (by affecting the metabolism of endogenous substrates), in addition to their receptor profile. A recent study suggests the implication of brain CYPs in cognitive, learning, memory processes and animal behavior. Thus, therapy of mental disorders should consider the dual role of some drug-metabolizing enzymes, whose polymorphism may affect not only drug metabolism but also patients vulnerability profile (Stingl 2018).

Studies using different approaches and methodologies aim to explain the engagement of brain cytochrome P450 in the endogenous metabolism and in consequence in brain physiology, pathology and pharmacology. Further research may allow for using this new knowledge on the functioning of brain CYP in developing more targeted, effective, and safer psychopharmacotherapy.

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