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Review

Role of brain cytochrome P450 (CYP2D) in the metabolism of monoaminergic neurotransmitters

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Abstract:
This article focuses on recent research on the cytochrome P450 2D (CYP2D) catalyzed synthesis of the monoaminergic neurotransmitters dopamine and serotonin in the brain and on the influence of psychotropic drugs on the activity of brain CYP2D. Recent *in vitro* and *in vivo* studies performed in rodents indicate that dopamine and serotonin may be formed in the brain *via* alternative CYP2D-mediated pathways, i.e., tyramine hydroxylation and 5-methoxytryptamine *O*-demethylation, respectively. The contribution of these alternative pathways to the total synthesis of brain neurotransmitters may be higher in humans and may be significantly increased under specific conditions, such as tyrosine hydroxylase and amino acid decarboxylase or tryptophan hydroxylase deficiency. These alternative pathways of neurotransmitter synthesis may also become more efficient when the CYP2D enzyme is mutated or activated by inducers (e.g., alcohol, nicotine, psychotropics), which may be of importance in some neurodegenerative or psychiatric diseases.
In addition to the previously observed influence of antidepressants and neuroleptics on CYP2D in the liver, the investigated drugs also produce an effect on CYP2D in the brain. However, their effect on brain CYP2D is different than that in the liver and is structure-dependent. The observed psychotropic drug-brain CYP2D interactions may be important for the metabolism of endogenous neuroactive substrates (e.g., monoaminergic neurotransmitters, neurosteroids) and for the local biotransformation of drugs. The results are discussed with regard to the contribution of CYP2D to the total synthesis of neurotransmitters in the brain *in vivo* as well as the possible significance of these alternative pathways in specific physiological and pathological conditions and in the pharmacological actions of psychotropic drugs.

Key words:
brain, cytochrome P450, dopamine, serotonin, antidepressants, neuroleptics

Introduction

Cytochrome P450 (CYP) is a hemoprotein enzyme that is present in the liver and extrahepatic tissues. The distribution of CYP isoforms in the body is isoform- and tissue-specific. In the brain it catalyzes local metabolism of drugs and endogenous substrates, such as steroids. The present state of knowledge on the biological significance and drug metabolism of brain CYP has recently been well described and discussed in a few extensive reviews [16, 30, 36]. The present article focuses on recent research on the CYP2D-catalyzed synthesis of the monoaminergic neurotransmitters dopamine and serotonin in the brain and on the influence of psychotropic drugs on the activity of brain CYP2D. The results are discussed regarding the contribution of CYP2D to the total synthesis of neurotransmitters in the brain *in vivo* as well as the possible significance of alternative pathways in specific physiological and pathological conditions and in the pharmacological actions of psychotropic drugs.

The functional role of the CYP2D subfamily in the brain

The CYP2D subfamily of cytochrome P450 enzymes consists of six isoforms in rats (CYP2D1–5 and CYP2D18) but has only one representative isoform, CYP2D6, in humans. The amount of CYP2D protein in rat hepatic microsomes increases with development until 14 weeks of age. However, in contrast to other rat CYP isoforms, the observed increase in CYP2D isoforms is not sex dependent [10].

CYP2D4 is regarded as the main CYP2D isoform in the rat brain, whereas CYP2D1 and CYP2D2 are the most abundant CYP2D isoforms in the liver [16]. The presence of CYP2D mRNA, protein, and activity in the rodent brain is predominantly observed in the basal ganglia (substantia nigra) and cerebellum [5, 26, 29]. Brain CYP2D isoforms, similar to their hepatic homologs, exhibit enzymatic competence toward endo- and xenobiotics, including psychotropic drugs [40]. The metabolism of codeine, amitriptyline, imipramine, and desipramine by rat brain CYP2D has been described [8, 21, 36]. Moreover, testosterone [1], clozapine and nefazodone [18, 22], resveratrol [35], nicotine [27, 43], and alcohol [28, 41] induce CYP2D in the brains of humans, monkeys, and rats, while MPTP attenuates the expression of mouse CYP2D22 [34].

It has been reported that CYP2D6 polymorphism may influence personality traits, as poor metabolizers of debrisoquine are more anxiety prone and less successfully socialized than extensive metabolizers of debrisoquine. Studies on the effect of the CYP2D6 genotype on resting brain perfusion support the hypothesis of a functional role of the enzyme in the human brain [25], suggesting the importance of CYP2D in the metabolism of endogenous neuroactive substrates in the brain [4, 17].

Brain CYP2D isoforms play an important role in the local metabolism of neurosteroids, and rat cytochromes CYP2D1 and CYP2D4 and the human protein CYP2D6 are reportedly involved in the metabolism (e.g., steroid 21-hydroxylation) of progesterone and allopregnanolone [24, 26]. Additionally, rat CYP2D18 mediates the ω-hydroxylation and epoxidation of arachidonic acid and may support the oxidation of dopamine to aminochrome, which is likely involved in the destruction of dopaminergic neurons in Parkinson's disease [38]. Several studies suggest that CYP2D may be involved in the metabolism of monoaminergic neurotransmitters in the brain. Hiroi et al. [23] showed that human CYP2D6 was capable of catalyzing the aromatic hydroxylation of tyramine to dopamine, and Yu et al. [42] demonstrated the ability of CYP2D6 to catalyze the *O*-demethylation of 5-methoxytryptamine to serotonin. Recent research on that subject was aimed at determining whether these reactions in fact occur in the brain.

Dopamine

The largest pathway in the brain dopaminergic system is the nigro-striatal pathway, combining the substantia nigra (neuronal group A9) with the striatum and controlling voluntary motor movement. Anatomically associated with this route is the mesolimbic pathway, which starts mainly from dopaminergic neurons in the ventral tegmental area (neuronal group A10) and connects them to the structures of the limbic system, which are involved in emotional behavior. Another route starting in the ventral tegmental area is the mesocortical pathway, which ends in different cortical areas and is engaged in intellectual processes. Directly related to the regulation of the endocrine system is the tuberoinfundibular pathway, which begins in the arcuate nucleus (neuronal group A12) and the perivenricular area of the hypothalamus and continues to the median eminence, releasing dopamine into the pituitary portal circulation.

In the classical pathway, dopamine is synthesized from phenylalanine, which is transformed into tyrosine *via* phenylalanine hydroxylase and then oxidized by tyrosine hydroxylase to dihydroxyphenylalanine (L-DOPA); the latter is further metabolized by aromatic amino acid decarboxylase into dopamine. The alternative way of dopamine formation in the brain may involve the hydroxylation of tyramine *via* CYP2D, which was first demonstrated for human cDNA-expressed CYP2D6 and liver microsomes [23]. Although tyramine derived from food does not cross the blood-brain barrier, it can be formed in the brain from phenylethylamine [3]. Hence, this pathway may constitute an alternative to tyrosine hydroxylase-mediated dopamine synthesis (Fig. 1).

In vitro studies

Tyramine is an endogenous compound that occurs in the brain as a trace amine in the form of *m*- and *p*-ty-