Drug-metabolizing cytochrome P450s in the brain

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Drug metabolism is traditionally thought of as a function of the liver. Although this remains essentially true, there is now evidence that drug-metabolizing enzymes are also located in extrahepatic tissues, such as the gut and lungs, where they have important functions. This commentary assesses the current knowledge of the presence and possible functions of drug-metabolizing cytochrome P450 enzymes in the central nervous system (CNS). As the brain is the target of centrally acting drugs, this review will also describe potential ways in which CNS expression may be particularly important in determining an individual's response to centrally acting substances.

Cytochrome P450 enzymes (CYPs) are phase I enzymes that are involved in the oxidative activation or deactivation of both endogenous and exogenous compounds such as drugs, environmental toxins and dietary constituents. Each CYP family member is designated by a number, each subfamily by a letter and each member of the subfamily by a second number (e.g., CYP2D6). This article will focus on the principal drug-metabolizing CYPs, most of which belong to families 1 to 4. These are mainly hepatic, but many of these CYPs also exist in other organs, including the brain. Much attention has been paid to CYPs in the liver because of their predominance there and because of the influence of drug-metabolizing CYPs on plasma levels of therapeutic drugs.

Brain CYPs were originally reported to occur at only 1% of the levels found in liver,[1] but many of these early reports treated the brain as a homogeneous organ, which is not the case. Brain regions differ tremendously in their cellular composition, cell density and function, and we now know that the expression pattern of brain CYPs is also extremely varied.[2] From some of our own studies, it is clear that the levels of CYPs in specific neurons can be as high or higher than levels in hepatocytes.[3] Although it is unlikely that brain CYPs contribute to overall clearance of xenobiotics, they are able to metabolize a variety of compounds, including many drugs that cross the blood–brain barrier to produce their pharmacological effects within the brain. Given their highly localized expression and extreme sensitivity to environmental inducers, they may contribute substantially to much of the observed interindividual variation in response to centrally acting drugs. They may also be responsible for some of the variation seen in side effects and toxicities of drugs that enter the

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CNS. Brain CYPs are also thought to participate in the metabolism of some neurotransmitters, endogenous steroids and neurosteroids; this aspect of their function may be important in influencing neural development and integration of overall brain function.

Identification and localization in the brain

Members of most CYP families have been identified in animal and human brains by a variety of methods. There is extensive information available on the regional and cellular distribution of most CYP families in rodent brain, but very little is known about human brain; only CYP2D6 has been mapped throughout the human brain.[4,5] In general, CYPs are distributed heterogeneously among different brain regions and are found in cell bodies and processes of neurons and often also in glial cells. Many of the CYP subfamilies have been observed at the blood–brain interface and in circumventricular organs (regions of the brain that are not protected by the blood–brain barrier)[6,7] such as the choroid plexus and posterior pituitary (e.g., CYP1A,[8–10] CYP2B[11] and CYP2D[12,13]). This may have evolved as a protection against harmful xenobiotics, but there is the caveat that these regions may also be exposed to toxic drug and steroid metabolites produced by local CYP activity. In rodents, CYP1A1 appears to be primarily expressed in regions of the blood–brain barrier,[8–10] but it has also been detected in other parenchymal brain regions.[9,14–16] CYP1A1 has also been identified in human brain[17,18] and localized to the cortical regions, midbrain, basal ganglia and cerebellum.[19] CYP1A2 has been found in most brain regions examined.[10,14,16] CYP1B1 has been shown to be present in various human brain regions, including the temporal lobe, putamen and blood–brain interface areas;[19–22] in most cases, CYP1B1 protein is localized to the nucleus.[23] CYP2B enzymes are heterogeneously distributed among brain regions in rodents,[3,16,24] with somewhat higher levels in evolutionarily older brain regions and areas of the blood–brain barrier, such as arachnoid, choroid plexus and other vascular areas.[3,11,25] This enzyme is primarily neuronal, with some astrocytic distribution in areas rich in neuronal fibre tracts (e.g., olfactory bulbs and corpus callosum).[11,26] CYP2B6 has been demonstrated in human brain,[27–29] and we have shown that its distribution is region-specific, with higher levels in the cerebellum and basal ganglia and lower levels in the cortical regions and hippocampus, and that its expression is primarily neuronal.[30] CYP2C is expressed constitutively in both rodent[31–33] and human brain;[19,34] in rats, CYP2C13 is expressed across a wide range of brain regions, including the basal ganglia, cortex, hippocampus and olfactory areas.[33–35] The expression of rodent CYP2D mRNA and protein is region-specific, with higher levels in areas such as the cerebellum, hippocampus and olfactory bulbs and lower levels in spinal cord, pons and medulla; it is expressed in both neuronal and glial cells.[12,13] In addition, individual CYP2D subfamily members (CYP2D1–6, 18) have different patterns of distribution among brain regions.[12,36] CYP2D6 has been identified in human brain,[4,28,37] and is expressed primarily in neurons of the cerebral cortex and hippocampus and in the Purkinje cells of the cerebellum.[4,5] The ethanol-metabolizing enzyme CYP2E1 is expressed constitutively in both rodent[38–41] (Lisa Angela Howard, MSc, and R.F.T., unpublished observations, University of Toronto, 2002) and human brains.[14,19,42] Expression is heterogeneous among brain regions and prominent in neurons of the cerebral cortex, dentate gyrus and the CA1, CA2 and CA3 regions of the hippocampus and in Purkinje cells and their processes in the cerebellum (L.A.H., S.L.M. and R.F.T., unpublished observations, 2002).[42] CYP2E1 expression and catalytic function have been demonstrated also in prenatal human brain, and this has implications in fetal alcohol syndrome.[43,44] Members of the CYP3A subfamily of enzymes are thought to metabolize approximately 50% of drugs in therapeutic use, and although they have been demonstrated in rodent[45,46] and human brain,[19,47] very little is known of their distribution. Human CYP3A5 has been localized in cells of the pituitary, where it is thought to be involved in the regulation of growth hormone secretion.[48] Members of the CYP4A and CYP4F subfamilies have been identified in rodent brain,[49] and subfamily members CYP4A2, CYP4A3 and CYP4A8 have been shown to have different distributions within the brain.[50]

Subcellular localization

In the liver, CYPs are located primarily in the endoplasmic reticulum or microsomal cell fraction. There is good evidence that some CYPs are also expressed in the plasma membrane,[51–53] the mitochondria[54] and in several of the continuous intracellular membrane compartments.[55,56] In the brain, it was observed early on that much of the CYP activity was found in the mitochondr-

ial subcellular fraction.[57] Although drug-metabolizing CYPs are traditionally found in the endoplasmic reticulum, a number of more recent studies have also shown the presence, inducibility and activity of several forms of drug-metabolizing CYPs in brain mitochondrial membrane fractions.[12,58–60] Two mitochondria-specific functional forms of CYP1A1 that are NH_2-terminal-cleaved versions of microsomal CYP1A1 have been identified in rat liver[61] and brain.[62] The protein structures of these P450MT2 forms are altered, allowing for specific targeting to the mitochondrial membrane. We and others have also demonstrated the expression of CYP enzymes in neuronal processes devoid of endoplasmic reticular membranes, particularly in the dendritic trees of Purkinje cells in the cerebellum.[30] The subcellular localization further emphasizes the uniqueness of brain-expressed drug-metabolizing CYPs compared with their hepatic counterparts.

Cautions in the identification of brain CYPs

Studies of the regional and cellular localization of CYPs in the brain do not always agree, both with respect to expression levels in brain regions and expression in specific cell types (i.e., neuronal or glial). There may be several explanations for this, one being the use of different techniques. Some studies report CYP mRNA levels only using reverse transcription – polymerase chain reaction (RT–PCR) or in situ hybridization, and some report CYP protein only using immunoblotting or immunocytochemistry techniques. Differences between findings using mRNA and protein may reflect that mRNA levels do not always predict protein levels because of variable rates of translation as well as other issues of mRNA and protein regulation (e.g., variable synthesis and degradation). In addition, in the CNS a protein and its mRNA are not necessarily expressed in the same part of the cell, and in some neurons with long axons projecting to other brain regions, the CYP mRNA can be located in the cell body and the CYP protein at the nerve terminal several millimetres away. Another cause of discrepancy can be that mRNAs are quite labile and so degradation, due to delays in removing and freezing brains, may differentially affect mRNA and protein. These discrepancies all point to the necessity of using multiple techniques for the detection and quantification of brain CYPs.

There are also disagreements between studies using the same techniques, such as immunoblotting or immunocytochemistry, that rely on the use of specific antibodies. The many antibodies and antisera available for the detection of CYPs vary greatly in their degree of specificity. In many cases, the use of antibodies with differing cross-reactivities and antigenic specificity is the source of discrepancy between reports. Most antibodies are developed against purified hepatic CYPs, partial peptides or ex vivo expressed CYPs, and the use of these antibodies assumes that brain CYPs are immunologically identical to hepatic CYPs, which may not necessarily be so. This has been a source of criticism of the literature on CYPs in the brain,[63] much of which incorporates the use of specific antibodies. However, this does not negate the presence of CYPs in the brain; our increasing knowledge of the genes and protein structures of brain CYPs can account for many of the observed differences between hepatic and brain CYPs from the same family. We know now that in many CYP families, specific members are expressed at higher levels in brain than in liver, with the same or similar catalytic properties to their hepatic counterparts (e.g., CYPs 2D4 and 2D18 in rat brain).[64–66]

Induction

It has long been known that brain CYPs are inducible by many of the same compounds that induce hepatic CYPs.[24,67] For example, phenobarbital can induce brain CYP2B1/2[16,68] and CYP3A1,[68] beta-napthoflavin,[10,16,62] 3-methylcholanthrene[69] and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin can induce CYP1A1,[9] phenytoin can induce CYP2B1/2,[70,71] steroid hormones can induce CYP2D[72] and ethanol can induce CYP2E1[38,39,42,73–75] (L.A.H and R.F.T., unpublished observations, 2002) and members of the CYP2C, CYP4A and CYP2D subfamilies.[76] In some cases, a compound's inductive effect is different in the liver and brain; for example ethanol induces CYP2B1 in rat liver but not in brain,[77] whereas nicotine induces CYP2B1 in rat brain but not in liver.[3]

The sensitivity of brain CYPs to regulation by endogenous and exogenous compounds may account for, in part, some of the variability in individual response to centrally acting drugs and some individuals' increased susceptibility to neurotoxic effects. There are several mechanisms whereby induction of brain CYPs can be detrimental. Increased CYP can modulate or reroute the metabolism of endogenous compounds such as testosterone by phenytoin-induced CYP2B.[71] High levels of CYP activity are associated with cellular oxidative stress.

High CYP2E1 activity is known to produce toxic free oxygen radicals, and ethanol induction of CYP2E1 has been shown to result in increased oxygen radical formation, oxidative stress and lipid peroxidation in rat brain[75] and cultured astrocytes.[74] In post-mortem brains of alcohol dependent individuals, we have observed intense immunological staining of CYP2E1 in cerebellum Purkinje cells and their processes (unpublished observations, 2002) and intense immunological staining of CYP2D6 in Purkinje cells and in hippocampal neurons compared with nonalcohol dependents;[4] both of these brain regions are highly susceptible to damage during chronic ethanol consumption.[78] Nicotine can also induce brain CYP2E1[79] (L.A.H. and R.F.T., unpublished observations, 2002), and given that many who are dependent on alcohol are also smokers, this effect of nicotine may contribute not only to central tolerance to alcohol in these individuals but also to an increased susceptibility to neuronal damage. Nicotine induces the nicotine-metabolizing enzyme CYP2B1 in rat brain,[3,80] and similarly, in human brain, nicotine-metabolizing CYP2B6 is higher in some brain regions of smokers than nonsmokers.[30]

Many CYPs activate carcinogens and produce toxic metabolites. Both CYP2E1 and CYP2B6 activate tobacco-smoke procarcinogens,[81] and CYP2B6 metabolizes a number of xenobiotics, such as methylenedioxymethamphetamine (MDMA or "ecstasy"),[82,83] cocaine[84,85] and the insecticide methyl-parathion[86] to toxic metabolites; this suggests that smokers, by virtue of increased CYP2B6 enzyme activity in specific brain regions and cells, may be more susceptible to neuronal pathologies.

Metabolism by brain CYPs

Although it is clear from the literature that there are some brain-specific forms of CYPs, some forms in the brain are identical to their hepatic isoforms (albeit at lower concentrations). What, then, is their metabolic importance? Brain CYPs have the ability to metabolize a range of endogenous and exogenous compounds, but because of the low levels of CYPs in the brain, metabolic studies have been technically challenging. CYP enzymatic activity has been reported in both rodent[24,87,88] and human[28,89,90] brain, but detailed kinetic studies on specific CYPs and their substrates are scarce. In rat brain, CYP2D1 kinetics for dextromethorphan in different brain regions have been described,[91] and the brain-specific CYP2D18 has been partially purified, and its activity toward the antidepressants imipramine and desipramine has been characterized.[64,92] In addition, brain microsomes have been shown to metabolize the same probe substrates used to assess specific hepatic CYP activity (e.g., 7-pentoxyresorufin for CYP2B1/2,[80,93,94] 7-ethoxyresorufin for CYP1A1/2,[79,93] *N*-nitrosodimethylamine and *p*-nitrophenol for CYP2E1[44,73] and dextromethorphan for CYP2D)[91,95,96] and substrates of known hepatic CYPs (e.g., bufuralol,[97] imipramine,[98] desmethylimipramine,[99] amitriptyline,[96] nicotine,[100,101] phencyclidine,[102] amphetamines[103,104] and neurotoxins such as organophosphorous insecticides[105]).

Exogenous substrates

Most evidence to date suggests that metabolic characteristics of brain CYPs are similar to their hepatic forms, with some exceptions where CYP forms exist in brain but not in liver. However, because of their low levels of expression in brain, it is unlikely that brain CYPs contribute to the overall metabolism and clearance of xenobiotics. Rather, their importance lies in their localization in specific brain regions and brain cells, where they are most likely involved in the in situ metabolism of xenobiotic drugs and toxins and endogenous neurotransmitters and neurosteroids. Plasma levels of drugs are not always good indicators of brain levels and therapeutic outcome,[106] and for neuroleptics and antidepressants, the correlations between blood levels and therapeutic effects are often poor.[107] CYP2D6 metabolizes many centrally acting psychoactive drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics and anticonvulsants.[108–110] Metabolism in the brain by this enzyme may have a profound influence on the on- and off-set of action and therapeutic efficiency of some of these drugs. For example, Chen and colleagues[103] have shown that at least the initial analgesic effects of codeine are due to morphine produced in the brain, not in the liver. In addition, as has been modelled by Britto et al,[111] the interindividual variation in response to these drugs, which is independent of plasma levels, could reflect interindividual differences in localized brain CYP2D6 metabolism.

Endogenous substrates

Neurotransmitters

An important role ascribed to brain CYPs is the metab-

olism of endogenous neurally derived or acting compounds, such as neurotransmitters and neurosteroids. Although CYP2D6 does not have a primary role in the synthesis of dopamine, it may have a modulatory effect on dopamine metabolism in the brain. CYP2D6 was found in close association with the dopamine transporter,[112] CYP2D enzymes have been found in dopaminergic cells in the rat substantia nigra[36] and CYP2D6[113,114] and rat brain-specific CYP2D18[115] have been implicated in dopamine metabolism. CYP2E1 is also found in dopaminergic cells of the rat substantia nigra,[35] and, recently, it was suggested that this enzyme may also be involved in dopamine metabolism.[116] Genetic polymorphisms in *CYP2D6* have been suggested to be associated with smoking behaviour,[117,118] and this modification may occur through the involvement of CYP2D6 in the dopaminergic pathway. Genetic defects in *CYP2D6* have been associated with Parkinson's disease,[119–122] which may be linked to the role of CYP2D6 in dopamine metabolism in the brain.[123,124] Genetic variation in *CYP2D6* has also been linked to Alzheimer's disease,[125–127] but it is still unclear whether the genetic variations are associated with the action of these enzymes in the brain or the liver.

Not only may CYPs contribute to the metabolism of neurotransmitters, but neurotransmitters, their precursors and their metabolites may have a modulatory effect on the catalytic activity of CYPs in the brain. It has been shown that tryptamine inhibits CYP2D6-mediated dextromethorphan O-demethylation,[114] serotonin and tryptamine inhibit CYP1A2 phenacetin O-deethylase activity[17] and 5-hydroxytryptamine and adrenaline inhibit diclofenac 4-hydroxylation by CYP2C9[128] in vitro. The effect of these indoleamines and catecholamines on CYP activity suggests that in the brain local drug metabolism by CYPs may be modulated or regulated by endogenous neurotransmitters, their precursors or metabolites and this may play a role in the observed interindividual variability in drug response.

Arachidonic acid

Arachidonic acid (AA) is metabolically activated to many endogenous compounds by cyclooxygenases, lipoxygenases and CYPs (e.g., CYP1A, 2B, 2C, 2D, 2E, 2J and 4A subfamilies.[32,115,129–135]). The main products of CYP metabolism are epoxygenase metabolites (14,15-, 11,12-, 8,9- and 5,6-epoxyeicosatrienoic acids or EETs), ω-terminal hydroxylase metabolites (20-, 19-, 18-, 17- and 16-hydroxyeicosatrienoic acids or HETEs) and lipoxygenase-like metabolites 15-, 12-, 9-, 8- and 5-HETEs.[136] EETs are metabolized primarily by the CYP2C subfamily[32,129,133] and possibly by CYP2D enzymes.[115] They are produced in astrocytes associated with cerebral microvessels and are involved in the local regulation of cerebral blood flow.[137–143] EETs are also produced in the pituitary and hypothalamus, where they stimulate the release of neuropeptides.[144–148] HETEs are formed primarily by the CYP4A subfamily in cerebral arteries[50,132,143,149] and are potent vasoactive agents.[50,141] Metabolism of AA by CYPs in the brain could have profound effects on cerebral blood flow, affecting cerebral function and contributing to cerebrovascular pathologies, and can also affect the release of neurohormones that influence many physiological functions.

Neurosteroids

Steroid hormones, which have a profound influence on the growth and development of the brain, are mainly synthesized in the adrenals and gonads and readily cross the blood–brain barrier. The brain also has the capacity to synthesize steroids, known as neurosteroids.[2,150–152] Endogenous neurosteroids contribute to the control of brain function and behaviour and may be involved in mental illnesses and in the activation of the immune system. Clinical studies have shown that neurosteroids are implicated in fatigue during pregnancy, post-partum depression, catamenial epilepsy and depressive and dementia disorders.[150] The initial stage of neurosteroidogenesis, the conversion of cholesterol to pregnenolone, is well characterized and is catalyzed by cytochrome P450 side-chain cleavage, the product of the CYP11A1 gene, and this can occur in both glial cells and in neurons.[151,153–155] Pregnenolone and dehydroepiandrosterone (DHEA) are further metabolized and inactivated in situ by a variety of enzymes, including CYPs, through the androgenic pathway to androstenedione, testosterone and estradiol and their derivatives, and through progesterone to potent neurosteroids such as 3α,5α-tetrahydroprogesterone. Cytochrome P450 aromatase, the product of the CYP19 gene, is important in the conversion of androgens to estrogens;[150] its activity and regulation have also been well characterized.

Members of the drug-metabolizing CYP subfamilies may also contribute in a modulatory capacity to the androgenic pathway. CYP1A can metabolize 17 β-estradiol,[156] DHEA and pregnenolone in mouse brain.[157–159]

CYP2B and possibly CYP2C can metabolize testosterone in rat brain,[71] and CYP2D can metabolize progesterone in rat brain.[160] CYP3A can metabolize testosterone in rat and mouse brain,[45,71] CYP3A9, a female-specific rat brain isoform of CYP3A, can metabolize testosterone, androstenedione, DHEA and, most efficiently, progesterone, a major female sex hormone.[161] CYP7B, a brain-specific CYP found primarily in the hippocampus of rat and mouse, is able to metabolize DHEA and pregnenolone.[162–164]

Although the drug-metabolizing CYPs are not the primary CYPs involved in the synthesis of these highly active neurosteroids from cholesterol within the brain, they appear to have the capacity to play a role in their local metabolism and elimination, as well as in the local inactivation of peripherally derived steroids. Consequently, any fluctuation in levels of brain CYPs through induction or suppression by xenobiotics or by endogenous substances such as steroid hormones,[72,165] may have a modulatory effect on local brain neurosteroid levels and result in changes in brain function (e.g., memory, learning or cognition) or in the development of neurological disorders or neuropathologies.

Summary

Most CYP subfamilies have been identified in brain, but there is much more information available on the distribution and metabolic activity of CYP subfamilies in brain of rodents than in humans, and what we do know still lags far behind our knowledge of hepatic CYPs. With the constant acquisition of data on the genetics, molecular structure and metabolic capacity of brain CYPs, we are increasingly able to investigate their role in the brain and the possible consequences of altered local metabolism. However, at this stage, the contribution of brain CYPs to local metabolism of drugs, toxins and endogenous compounds is still speculative, as is the role for these CYPs in modulating brain function and in the development of brain diseases. Much investigative work remains to be done to firmly establish the links between the presence of CYPs in brain, their function in this highly heterogeneous and complex organ and the consequences on overall brain function and health.

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