CYP2D6, its Genetic Polymorphism and the Brain

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Abstract
Cytochrome P450 system comprises of several families of non-specific monoxygenases that catalyze Phase-I biotransformation reactions of an extensive list of drugs. The genes encoding for these Cytochrome P450 (CYP) enzymes are highly polymorphic. Further, these enzymes are susceptible to inhibition or induction by various drugs. So far, these enzymes have been extensively studied in context to drug-drug interactions and drug-gene interactions. However, their role in different organs other than liver and intestines during health and disease remain largely unknown. Among these CYP enzymes, CYP2D6 represents a highly polymorphic isozyme that has low content in the liver compared to other isozymes, yet metabolizes a significant proportion of the clinically used drugs. This mini review explores the role of CYP2D6 in the brain during health and disease. CYP2D6 is expressed in different regions of the brain and also, its expression varies among different brain cells. CYP2D6 and its genetic polymorphism have important impact on the normal brain functions ranging from brain metabolism, cerebral perfusion to cognition and behavior. CYP2D6 and its genotypes are also associated with the risk of Parkinson’s disease, Schizophrenia, and depression. Since, CYP2D6 activity can be modulatable, therefore, it represents a potential modulatable therapeutic target that can be used to treat various neuropsychiatric, neurodegenerative and cerebrovascular diseases.

Keywords: Cytochrome P450, CYP2D6, Genetic Polymorphism, allele, neurodegeneration, stroke

Introduction
Cytochrome P450 system comprises of a superfamily of heme containing mono-oxygenases that have evolved over 400 – 500 million years ago to detoxify the chemicals contained in the plants by the animals (Park, Pirmohamed, and Kitteringham 1995). Drug biotransformation is a fundamental process that involves sequential or competitive chemical reactions categorized as Phase I and Phase II reactions. The basic purpose of these drug biotransformation reactions is to convert the drug into polar, water soluble and easily excretable metabolites that can be readily excreted out of the body (Chaudhry et al. 2014). Cytochrome P450 mono-oxygenases play a major role in the Phase I drug oxidation reactions and account for nearly 75% of the total drug metabolism (Chaudhry et al. 2014). Cytochrome P450 enzymes derived their name due to the production of spectral peak around 450 nm when reduced and bound to carbon monoxide (Chaudhry et al. 2014). These enzymes make use of the NADPH and oxygen to modify their substrates and are conserved in diverse species throughout the nature ranging from archaeabacteria to humans (Black, O’Kane, and Mrazek 2007, Guengerich 2002).

There are around 57 genes that encode for human cytochrome P450 enzymes (CYPs) that are grouped into 18 families and 43 subfamilies based on sequence similarities (Preissner et al. 2013). Out of these families, CYP isoforms from CYP1, 2 and 3 families are responsible for metabolizing nearly 80% of the clinically used drugs (Ingelman-Sundberg 2004a Figures 1 & 2). These CYP isoforms include CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,
Figure 1. Relative content of different Cytochrome P450 isozymes in human liver.

CYP2D6, CYP2E1, CYP3A4 and CYP3A5 (Zhao et al. 2021). An important feature of concern is that these CYPs display variations in the expression and activity, and these variations are not limited to individuals, but are also evident among different ethnicities (Zhao et al. 2021). These variations are due to the genetic polymorphisms in the genes encoding these CYPs (Ingelman-Sundberg et al. 2007). More than 350 functionally polymorphic CYPs have been identified so far (Zhao et al. 2021). These polymorphisms lead to variable internal exposures from the drugs resulting in either drug toxicity or therapeutic failure (Chaudhry et al. 2014). These CYP genetic polymorphisms have led to characterize them into functionally distinct four phenotypic categories based on their in vivo drug metabolizing capacity (Ingelman-Sundberg et al. 2007). These four categories are as follows:

- **Extensive metabolizers** (Normal metabolizers): carrying two functional alleles with normal activity for a particular CYP P450 isoform
- **Poor metabolizers**: lacking functional genes leading to significantly reduced to no enzyme activity.
- **Intermediate metabolizers**: carrying one functional and one defective allele or inheriting two partially active alleles resulting in a metabolic activity between poor and normal metabolizers.
- **Ultrarapid metabolizers**: carrying more than two active copies of the CYP P40 enzyme resulting in metabolic activity that is significantly higher than normal metabolizers.

Knowing the genetic fingerprints for these CYP isoforms is of paramount importance and can guide the drug therapy according to the individual needs. For instance, ultrarapid metabolizers may significantly inactivate the normal administered dose leading behind no therapeutically active drug resulting in therapeutic failures. Whereas, poor and intermediate metabolizers may be susceptible to confront the drug toxicities due to inability to metabolize the active parent drug into inactive metabolites (Chaudhry et al. 2014, Ingelman-Sundberg 2004b, Ingelman-Sundberg et al. 2007). In addition to these genetic polymorphisms, various drugs can also induce the synthesis or inhibit a particular CYP isoform, creating an additional parameter of consideration while optimizing the therapy for an individual patient (Doan et al. 2013).

Most of the studies regarding the CYPs have been done from the point of view of drug development and predicting the drug toxicity or inefficacy (Guengerich 2002). However, studies exploring their role in health and disease in various tissues other than liver are still lacking. Among the other CYPs, CYP3A4 and CYP2D6 account for 50% of the CYPs mediated drug metabolism, and
Figure 2. Relative proportions of the different clinically used drugs metabolized by different Cytochrome P450 isozymes.

CYP2D6 alone accounts for nearly 25% of the metabolism of the clinically used drugs despite its low content amongst the other CYP isozymes (Chaudhry et al. 2014, Zhao et al. 2021). Further, in addition to its expression in the liver which remains constant after birth, the expression of CYP2D6 increases within the brain (Zhao et al. 2021). After a brief overview of the CYP P450 system, the rest of this mini review will provide an overview of the significance of the CYP2D6 expression in the brain and its implications during health and disease.

CYP2D6
CYP2D6, also known as debrisoquine/sparteine hydroxylase, is encoded by a gene localized on chromosome 22 comprising of nearly 4.3 Kbps (22q13.2) (Taylor et al. 2020, Bertilsson et al. 2002). In this gene, nine exons encode for the CYP2D6 protein, which upon translation localizes to the endoplasmic reticulum (Taylor et al. 2020). CYP2D6 is a highly polymorphic gene with more than 100 allelic and sub-allelic variants (Nofziger et al. 2020). Interestingly, the polymorphic nature of the CYP2D6 not only encompass poor metabolizer status, but is also extended to the other extreme with Ultrarapid metabolism (Bertilsson et al. 2002). Ultrarapid metabolizers of the CYP2D6 have been shown to carry up to 13 copies of the active gene (Bertilsson et al. 2002). CYP2D6 accounts for the metabolism of nearly 25% of the clinically used drugs and almost 100 commonly used drugs in the clinics are the substrates for this isozyme despite its low content (2 – 4%) among other CYP isozymes in the liver (Bertilsson et al. 2002, Chaudhry et al. 2014, Williams et al. 2018) (Fig. 1 and Fig. 2). The expression of CYP2D6 is very high in the liver, intestine, lymphoid cells and the brain (Taylor et al. 2020). This enzyme has been extensively studied for its role in the drug metabolism and even for the drugs having important effects on the brain e.g., antidepressants and antipsychotics, however, studies exploring its expression and putative role in the brain are scarce and are currently underway.

CYP2D6 and the brain
Expression of CYP2D6 in brain
The levels of CYP2D6 expressed in the brain are less than that of the liver. However, among other CYPs the expression of CYP2D6 is above 5% of the total P450 CYPs expressed in the brain (Dutheil et al. 2009). CYP2D6 has been shown to be expressed in all major regions of the brain selected for expression analysis and
the regions showing higher total transcripts in decreasing order were putamen, caudate nucleus, frontal lobe, nucleus accumbens, cortex, substantia nigra, hippocampus, insula and corpus callosum etc. (Dutheil et al. 2009). Immunohistostaining revealed low expression of CYP2D6 in the neuronal cells, whereas its expression was higher in astrocytes including glia limitans in the frontal cortex (Dutheil et al. 2009). Moderate expression of CYP2D6 has been observed in the dentate gyrus, CA1 through CA3 and CA4 pyramidal neurons (Dutheil et al. 2009). In the cerebellum, soma and dendrites of the purkinje cells showed highest expression of the CYP2D6 and similarly, astrocytes in the molecular layer, white matter and glia limitans displayed higher expression of CYP2D6 (Dutheil et al. 2009). This unequal distribution of CYP2D6 shows a potential role in brain function and previous studies have shown that CYP2D6 is implicated in the endogenous metabolism of anandamide and neurotransmitters (Snider et al. 2008, Yu et al. 2003, Yu, Idle, and Gonzalez 2004).

CYP2D6 and personality traits
The role of CYP2D6 in the brain is further emphasized by the reports suggesting its impact on personality traits and its associations with Parkinson’s disease and schizophrenia (Dorado, Peñas-Lledó, and Llerena 2007). CYP2D6 is hypothesized to provide neuroprotection against extrapyramidal and psychotic symptoms and its expression is higher in the brains of smokers owing to induction by nicotine (Dorado, Peñas-Lledó, and Llerena 2007). CYP2D6 genotype has a potential influence on the personality. For instance, CYP2D6 poor metabolizers are associated with more anxious behavior and less socialization compared to extensive metabolizers (Llerena et al. 1993). However, CYP2D6 poor metabolizers have been also found to score less on type A personality style compared to extensive metabolizers suggesting that this genotype may protect against psychopathology induced by stress (Gan et al. 2004). Also, the poor metabolizers of CYP2D6 exhibited lower scores on the temperamental trait of harm avoidance suggesting a less susceptibility to anxiety in depressive patients compared to normal metabolizers of CYP2D6. Furthermore, these poor metabolizers of CYP2D6 also showed low scores on fear of uncertainty, fatigability and shyness (Roberts et al. 2004). A group of female poor metabolizers of CYP2D6 showed an association with a personality trait that is linked with competence, achievement striving and resilience (Kirchheiner et al. 2006). Interestingly, CYP2D6 genotype also influences the levels of brain neurotransmitters especially serotonin and dopamine, which are associated with different behavioral traits (Dorado, Peñas-Lledó, and Llerena 2007). Additionally, CYP2D6 polymorphism may be linked to various behavioral traits through modulating the activity of neuroactive steroids such as progesterone and derivatives, and tyramine (Dorado, Peñas-Lledó, and Llerena 2007). Owing to the ability of CYP2D6 to modulate the serotonergic and dopaminergic activity in the brain, it may be likely that CYP2D6 is implicated in the vulnerability to schizophrenia (Dorado, Peñas-Lledó, and Llerena 2007). CYP2D6 also plays an important role in the regeneration of serotonin from 5-methoxytryptamine and poor metabolizers have been shown to present with lower levels of serotonin (Dorado, Peñas-Lledó, and Llerena 2007, Yu, Idle, and Gonzalez 2004). However, different studies have shown that inheriting an ultra-rapid metabolizer genotype characterized by inheriting multiple copies of the enzyme is associated with a severe type of suicidal behavior (Sim, Kacevska, and Ingelman-Sundberg 2013).

CYP2D6 and brain perfusion
Brain perfusion can serve as an index of cerebral activity when measured during rest (Kirchheiner et al. 2011). But a significant degree of variation exists in the cerebral perfusion. Intriguingly, a study demonstrated the impact of CYP2D6 polymorphism on the cerebral perfusion, since, CYP2D6 is implicated in the endobiotic metabolism. The authors of the study specifically focused on two brain regions i.e., thalamus and hippocampus to measure the cerebral perfusion and the impact of CYP2D6 genotype. It was quite interesting to note that the poor metabolizers of the CYP2D6 had 15% higher perfusion at rest in the thalamus. However, there was no difference in the thalamic activation depending upon the CYP2D6 genotype. A weak effect of the CYP2D6 activity was observed in the hippocampus. The impact of CYP2D6 genotype was also evident collectively on the whole brain sample regarding cerebral blood flow and interestingly, it showed variations with respect to the CYP2D6 allele activity (Kirchheiner et al. 2011).
CYP2D6 and other roles in brain

Intriguingly, a study showed the impact of CYP2D6 genotype on the working memory task which was evident in the fusiform gyrus and the precuneus. The effect of CYP2D6 genotype was also detected in the cuneus in an emotional face matching task. In both of these tasks increased activation correlated with higher CYP2D6 activity suggestive of the potential role of CYP2D6 in cognitive processes (Stingl et al. 2012). Conversely, an fMRI based study of the resting brain perfusion images was found to predict the CYP2D6 ultrarapid and poor metabolizer status (Napolitano et al. 2017). A recent investigation has shown decreased cognitive efficiency in rapid metabolizers when compared to poor metabolizers in on-task attentional processes (Viviani et al. 2020). CYP2D6 genotype also influences the metabolic demands in the brain as 5% decrease in glucose uptake was observed in the insular cortex of the intermediate metabolizers compared to extensive metabolizers (Joffe et al. 2012).

CYP2D6 genotype may be used to predict the risk of Parkinson’s disease (PD) as poor metabolizers of CYP2D6 have high risk of developing PD and even this risk further increases in the presence of pesticide exposure (McCann et al. 1997, Elbaz et al. 2004). The neuroprotective effects of CYP2D6 are believed to stem from its ability to detoxify neurotoxins such as 1,2,3-tetrahydroisoquinolines, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), β-carbolines and modulate serotonin and dopamine levels (Mann et al. 2012). Interestingly, CYP2D6 expression increases in different brain regions (frontal cortex, substantia nigra, cerebellum) normally with age, but PD patients had lower expression of CYP2D6 in these regions. Surprisingly, PD patients exhibit similar expression of CYP2D6 to that of controls in the substantia nigra or caudate, the areas most affected in PD and this is owing to astrogliosis or intense non-astrocytic CYP2D6 expression in these regions (Mann et al. 2012). Furthermore, there is also an evidence for the mitochondrial localization of the CYP2D6 in addition to the endoplasmic reticular expression and interestingly, it contributes to the activation of neurotoxins instead of microsomal CYP2D6 (Chattopadhyay et al. 2019).

These pieces of evidence suggest that CYP2D6 and its polymorphism has important impact on brain functions, in addition to, the relatively well established pharmacogenetic effects. Since, CYP2D6 activity can be modulatable through the use of CYP2D6 inhibitors or inducers, it might be possible to modulate the brain functions for potential therapeutic benefits. Therefore, CYP2D6 represents a potential therapeutic option for the treatment of psychiatric disorders such as schizophrenia, depression and neurodegenerative disorders such as Parkinson’s disease. As already mentioned above, CYP2D6 activity correlates with cerebral perfusion of the blood, therefore, it might serve as a potential modulatable therapeutic target against cerebral ischemia due to ischemic stroke or hemorrhagic stroke induced cerebral vasospasms.

Conclusions

CYP2D6 is expressed in different regions of the brain and modulates various brain functions. Therefore, it might serve as a potential modulatable therapeutic target for the treatment of neuropsychiatric, neurodegenerative and cerebrovascular diseases.

Conflict of interest

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SRC has conceived the idea and drafted the initial manuscript. MAT and MA critically reviewed the manuscript for intellectual content. All the authors have read and approved the final version of the manuscript.

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