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Pharmacogenomics of Cytochrome P450 Dependent Metabolism of Endogenous Compounds: Implications for Behavior, Psychopathology and Treatment

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Abstract

Mood and anxiety disorders are a major burden to the society today but still the pathophysiology behind these disorders is largely unknown and the pharmacotherapy available today is far from sufficient, with relatively low remission rates. Recent results regarding the action of CYP2C19 and CYP2D6 in the CNS suggest associations between suicidality, anxiety and other stress-related disorders and such CYP enzyme polymorphisms. Knowledge about the CNS specific action of these enzymes might in the future provide an increased understanding of the pathogenesis and pathophysiology of these disorders. Here we present an update of the research carried out in human and animal models with focus on the roles of CYP2C19 and CYP2D6 for brain development and function mediated by the metabolism of endogenous compounds.

Keywords: CYP2D6; CYP2C19; Psychopathology; Depression; Polymorphism; Suicidality; Anxiety

Introduction

The human genome carries 57 genes encoding active cytochrome P450 enzymes. About 6-8 of these genes encode P450 enzymes active in the metabolism of clinically used drugs [1,2]. A large majority of these genes are polymorphic and alleles causing defective, diminished, qualitatively altered or increased drug metabolism have been described (See The Human Cytochrome P450 (CYP) Allele Nomenclature Database; www.cypalleles.ki.se). This variation is of importance for explaining interindividual differences in drug metabolism, drug efficacy and adverse drug reactions. Because of the major function for metabolism of exogenous compounds in the hepatic detoxifications processes these polymorphisms do not cause any major alterations in the phenotype of the individual. Accordingly no major phenotype in KO mice for any cytochrome P450 gene encoding hepatic enzymes active in drug metabolism has been described, although phenotypic changes have been seen in transgenic mice overexpressing some Cyps. The endogenous role in metabolism of the P450s in question is mainly related to oxidation of cholesterol, bile acids, steroid hormones and fatty acids [1]. Thus in mice transgenic for *CYP3A4*, disturbances in lactation of female mice are seen due to increased estradiol metabolism [3]. The area of endogenous roles of the P450 polymorphism has however not been completely unraveled. Phenotypes not obvious might however be related to such polymorphisms and indeed many examples of associations between such genetic variation and altered endogenous functions and phenotypes have been presented in the literature. Specific interesting aspect concerns the endogenous roles of cytochrome P450s expressed in the brain [4]. We here present recent results obtained regarding the CNS specific functions of CYP2D6 and CYP2C19 and possible implications for CNS disease.

Substrates	CYP2C19	CYP2D6
Exogenous	Amitriptyline Clomipramine Citalopram Diazepam Mephenytoin Moclobemide Sertraline	Antiarrhythmics Antipsychotics Beta blockers Codeine Dextromethorphan SSRIs Tricyclic antidepressants
Endogenous	Arachidonic acid Docosahexaenoic acid Eicosapentaenoic acid Estradiol Estrone Progesterone Testosterone	Anandamide 5-Methoxytryptamine Pregnenolone Progesterone Serotonin Testosterone Tyramine

Table 1: Some CNS active substrates for CYP2C19 and CYP2D6.

CYP2D6

CYP2D6 is highly polymorphic and in Caucasians 7-10% are defective for expression of this enzyme (PMs) whereas 2-10% carry more than one functionally active *CYP2D6* gene on each allele and are ultra-rapid metabolizers (UMs) [5,6]. The enzyme has been suggested to be active in the metabolism of the endogenous compounds 5-methoxytryptamine, anandamide, progesterone and tyramine [4] (Table 1). CYP2D6 mRNA and protein has been found in neurons in numerous human brain areas, including e.g. thalamus, hypothalamus, hippocampus, substantia nigra, cerebellum, and in several layers of the frontal neocortex [7,8]. The fact that CYP2D6 is expressed in the brain raises questions regarding its potential functions within the brain and more specifically in the neurons. It is likely that regional expression of CYP2D6 affects local metabolism of CNS-acting drugs metabolized by the enzyme that in turn can affect treatment outcome. However, CYP2D6 has in the last decade also been suggested to be involved in endogenous metabolism of e.g. trace amines and neurosteroids, which implicates a role in normal brain homeostasis as well. Several studies have shown that CYP2D6 expressed in liver and brain can metabolize tryptamines into both serotonin and dopamine [9,10], and furthermore

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metabolize the neurosteroid progesterone [11,12]. Further supporting this hypothesis is the *CYP2D6* transgenic mouse model, displaying brain expression of the enzyme, displaying significantly higher serotonin levels in several brain regions, including the cerebellum and hippocampus [13].

In vitro studies also suggest that *CYP2D6* is involved in the transformation of other neurosteroids like testosterone [14] and pregenolone [15]. Additionally, *CYP2D6* has also been suggested to be involved in the endocannabinoid system within the CNS due to its ability to metabolize anandamide and its derivatives [16]. The physiological significance of such metabolism is however still unclear and the affinities for *CYP2D6* enzyme by the compounds suggested might in many cases not be appropriate for significant metabolism under physiological conditions.

Psychopathology and behavior

Associations between *CYP2D6* genotypes and personality traits were one of the first indications that CYP2D6 might have endogenous functions apart from its important role in drug metabolism.In one of the first reports it was shown that poor metabolizers displayed higher impulsivity-related traits [17]. Further studies have found similar traits among poor metabolizers [18] whereas others have found poor metabolizers to be more anxiety-prone and less successful in socialization, when compared with extensive metabolizers [19,20]. The inconclusive results could be explained by the different ethnicities of the populations and methods used but do however suggest that CYP2D6 might have important endogenous functions in the human brain.

Furthermore, the ultra-rapid metabolizer phenotype where the subjects carry 3 or more active *CYP2D6* genes has been associated with higher suicidal risk [21,22] as well as increased suicidal behavior among individuals with eating disorders [23]. The number of active *CYP2D6* genes has been associated with higher perfusion rates in the thalamus and the right hippocampus among healthy human subjects during resting [24] and lower perfusion rates in the cuneus and precuneus during cognitive tasks [25]. This provides an interesting mechanistic link to the findings concerning a relationship to suicidality, although as a whole these results have to be reproduced in larger independent cohorts before causality can be concluded.

Interestingly, an increased risk for Parkinson's disease among *CYP2D6* poor metabolizers was recently described in a large meta-analysis [26]. Poor metabolizers furthermore displayed a better capacity to vigilance and alertness when exposed to a specific assignment and performed better in spatial memory tasks [27]. The displayed differences in neurocognitive function and perfusion rates display direct effects of *CYP2D6* polymorphism on brain function. However, the basis for a CYP2D6 dependent influence on brain function remains unknown. CYP2D6 is very active in the metabolism of CNS active drugs, preferentially those containing basic nitrogens, so it might be suggested that the endogenous CYP2D6 substrates have similar structures and act as ligands to receptors within e.g. the serotonergic and dopaminergic systems.

CYP2C19

CYP2C19 is an important drug metabolizing enzyme involved in the metabolism of approximately 7-10% of all drugs used on the market today demonstrating broad substrate specificity [2,28]. The *CYP2C19* gene, like many other CYP genes, is highly polymorphic. This polymorphism influences both blood plasma levels of drugs metabolized by CYP2C19 but also treatment outcome [29-32]. Like CYP2D6, CYP2C19 has a broad substrate specificity and is involved in the metabolism of many different classes of psychotropic drugs, including selective serotonin reuptake inhibitors e.g. sertraline [33,34] and citalopram [35,36], tricyclic antidepressants like amitriptyline [37] and clomipramine [38], and the monoamine oxidase inhibitor moclobemide [39]. CYP2C19 is furthermore involved in the metabolism of benzodiazepines e.g. diazepam [40] and the anticonvulsant drug mephenytoin [41,42] (Table 1).

Most studies investigating the effects of *CYP2C19* polymorphism have been focused on the impact of drug plasma levels and related issues and therefore relatively little is known regarding endogenous effects of the *CYP2C19* genotypes without drug challenge. However, some studies have suggested that *CYP2C19* polymorphism also could play a role in predicting personality traits and depressive symptoms [43-45]. The suggested effect of *CYP2C19* polymorphism on personality traits and depressive symptoms proposes that CYP2C19 is involved in the metabolism of endogenous substrates as well.

Endogenous substrates

Indeed, relatively few studies have investigated if CYP2C19 could be involved in the metabolism of endogenous compounds and due to its broad substrate specificity this is likely. *In vitro* studies performed in human liver microsomes have suggested CYP2C19 to be involved in the metabolism of steroid hormones. CYP2C19 is shown to effectively catalyze the 17β-hydroxy dehydrogenation of estradiol into estrone [46] and furthermore to contribute to the formation of the estrone metabolite 16α-OH-estrone [47]. CYP2C19 has been suggested to metabolize progesterone into mainly 21-OH-progesterone but also to some extent 16α-OH-progesterone [48]. Besides being involved in the metabolism of estradiol and progesterone, CYP2C19 has also been shown to oxidize testosterone into mainly androstenedione, but also to a lesser extent, 6β-, 16β-, and 2β-OH-testosterone [48]. In conclusion, several studies show that CYP2C19 can metabolize different steroid hormones. However, effects connecting *CYP2C19* polymorphism with hormone levels have so far not been investigated *in vivo*.

Most of these steroid hormones are known to be active and also synthesized within the CNS. Their functions are diverse and important for normal brain development and for postnatal brain maturation and plasticity [49-51]. Thus, there might be a role for CYP2C19 in the metabolism of CNS localized steroid hormones.

Besides steroids, CYP2C19 has been suggested to be involved in the metabolism of several different polyunsaturated fatty acids e.g. arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid [52,53]. Some studies have also proposed that CYP2C19 is important in the metabolism of the exogenous cannabinoid cannabidiol, thus suggesting that other endogenous cannabinoids could be potential substrates as well [54,55]. However this area of research need to be extended and confirmed before any firm conclusions can be drawn. Nevertheless the proposed substrates are highly relevant and the CYP2C19 dependent metabolism of these might possibly explain the associations seen between *CYP2C19* polymorphism and human phenotypes as further emphasized below.

Psychopathology and behavior

The first studies on associations between *CYP2C19* polymorphism and human phenotypes, without a drug challenge, investigated personality traits using the Temperament and Character Inventory (TCI) [43,44]. It was initially suggested, in a cohort of healthy Japanese, that CYP2C19 homozygous extensive metabolizers had a lower

score in harm avoidance (HA) compared to heterozygous extensive metabolizers and poor metabolizers [44]. This report proposes that higher CYP2C19 enzymatic activity is associated with a more carefree, outgoing, and optimistic personality. Other studies have furthermore shown that high scores in HA are strongly associated with depression and can also predict MDD [56-58].

Another study, also investigating healthy Japanese subjects, found that female CYP2C19 poor metabolizers scored significantly lower on the dimensions reward dependence, cooperativeness, and self-transcendence, compared to extensive metabolizers. Individuals with low scores in cooperativeness are more socially intolerant, unhelpful, and opportunistic [43] and has also been connected to a current state of depression [56]. Individuals with low scores in reward dependence are on the other hand more cold, practical, and withdrawn and low scores in self-transcendence are associated with an impatient, unimaginative, and proud personality [43].

The results from these two studies are rather inconclusive, but do however reveal some common aspects since CYP2C19 poor metabolizers displayed high scores in HA and low scores in cooperativeness, previously shown to associate with depression. However, the observed gender differences and low number of participants encourages for these studies to be reproduced in larger cohorts and also in other ethnic groups.

Apart from being connected to personality traits *CYP2C19* polymorphism has also been associated with depressive symptoms. Subjects from the Swedish twin registry were assessed using the center for epidemiologic studies depression (CES-D) scale. The CES-D scale measures depressive symptoms and consists of four subscales that together form the total score (T1) with higher scores indicating higher levels of depressive symptoms during the last week [59]. This study suggests that poor metabolizers have lower depressive symptoms based on their significantly lower T1 scores, and lower scores on the subscales depressed mood, and psychomotor retardation and somatic complaints, compared to extensive metabolizers [45].

Brain expression of CYP2C19

Expression of CYP2C19 in humans has long been thought to be restricted to the liver and small intestine [60-62]. Recent preliminary studies of human fetal brain samples did however show relatively high cortical expression levels of CYP2C19, around 0.5% of that seen in adult liver. Transgenic mice for the human *CYP2C19* gene also displayed

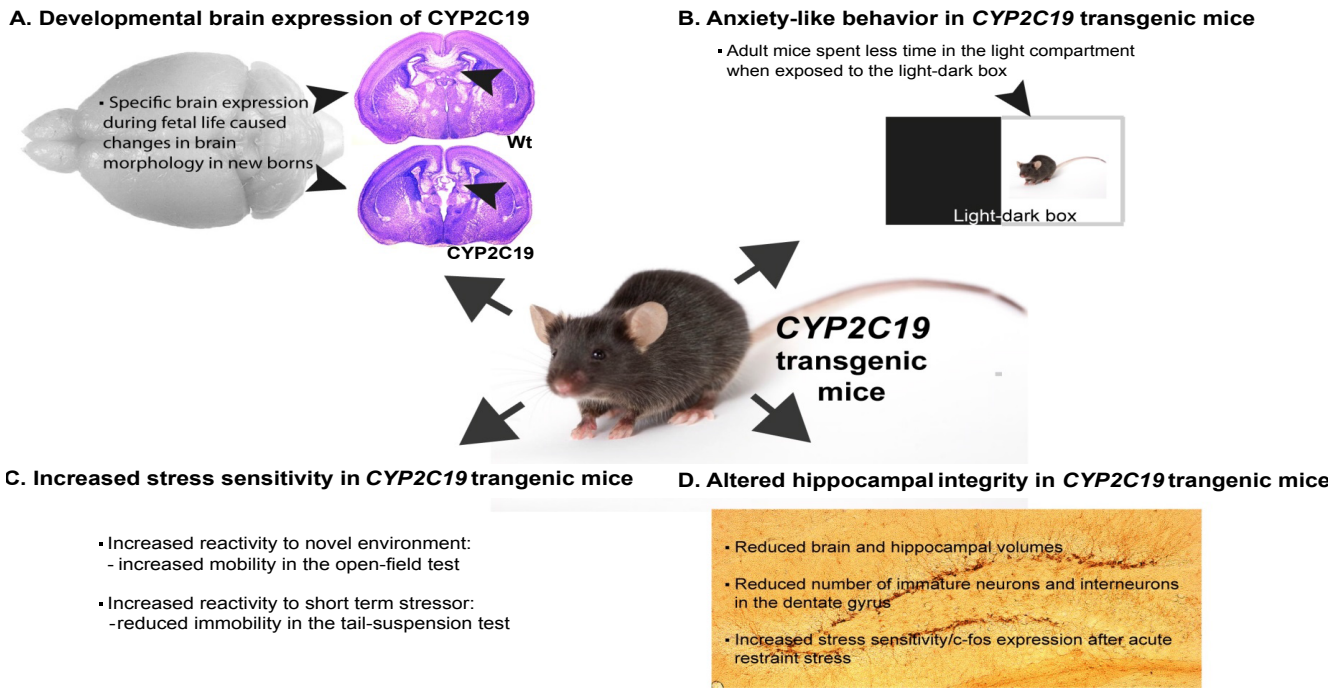

Figure 1: Phenotypes described for the human *CYP2C19* transgenic mouse.

A. *CYP2C19* mRNA expression was unexpectedly seen specifically in the brain during embryonic and fetal development in the *CYP2C19* transgenic mouse. Brain *CYP2C19* mRNA expression peaked at embryonic day 18, with a 6-fold higher expression in brain compared to liver but the expression silenced after birth. Preliminary data indicated that this brain expression of CYP2C19 occurs during fetal development of human brain as well. The morphological brain phenotype at postnatal day 0 in mice homozygous for the genetic insert (CYP2C19) compared to a Wt brain is presented. The *CYP2C19* homozygous mice displayed an extensive morphological phenotype with complete callosal agenesis and a less developed and smaller hippocampal formation compared to Wt litter mates, changes indicated by arrows in the images.
B. Adult *CYP2C19* transgenic mice displayed an increased anxiety-like behavior as measured by the light-dark box. They spent significantly less time in the light compartment compared to Wt litter mates, thus indicating an anxiogenic-like phenotype.
C. Adult *CYP2C19* transgenic mice displayed an increased reactivity to stressful situations as displayed by their behavior in the tail-suspension test and in the open-field. They had an increased total distance travelled in the open-field compared to Wt controls and a significant reduction in immobility time was recorded in adult transgenic mice in the tail-suspension test.
D. Adult *CYP2C19* transgenic mice showed a smaller brain and hippocampal volumes as measured by magnetic resonance imaging. Furthermore was the neuron population within the hippocampal formation severely affected with e.g. reduced number of immature neurons. In response to acute stress an increased neuronal activation (increased c-fos expression) was observed in the hippocampus of the transgenic mice thus indicating an altered stress response of the hippocampus in these mice. All data are adapted from [62].

CYP2C19		CYP2D6	
UMs	PMs	UMs	PMs
In transgenic mice disturbance of brain development including smaller hippocampus	Decreased depressed mode	Higher suicidal risk	Higher risk for Parkinson's disease
In transgenic mice increased anxiety and stress sensitivity	Higher score in harm avoidance	Increased suicidal behavior	Higher impulsivity-related traits and more anxiety prone
	Lower score in cooperativeness	Higher perfusion rates in thalamus and hippocampus	Better capacity to vigilance and alertness
			Perform better in spatial memory tasks

Table 2: Phenotypes described among subjects being poor metabolizers (PMs) or ultrarapid metabolizers (UMs) for CYP2C19 and CYP2D6 (For further explanations see text).

specific brain expression of CYP2C19 during fetal life that is completely silenced after birth [63]. This suggests that CYP2C19 expression occurs as a peak in the CNS during fetal life and might then exert endogenous functions of importance for the development of the brain.

CYP2C19 transgenic mouse model

The transgenic mouse model for the human *CYP2C19* gene displays some interesting phenotypes. High expression of the enzyme is lethal, with pups dying only a few days after birth. These mice display complete callosal agenesis and a severely underdeveloped hippocampus. Mice with fewer copies of the insert, possibly more closely resembling the expression seen in human rapid metabolizers, displayed no obvious neonatal disturbances of brain morphology. These mice did however show a behavioral phenotype in adult life, with increased stress sensitivity and increased anxiety-like behavior, as described in Figure 1 [63]. Stressful life events and stress sensitivity are major risk factors for psychiatric disease making this model highly interesting for investigating systems that are involved in regulating the stress response [64,65]. The *CYP2C19* transgenic mice furthermore showed a hippocampal phenotype as adults, with a smaller and more stress sensitive hippocampal formation that furthermore contained a drastically reduced number of immature (double-cortin positive) neurons. The hippocampal formation has many critical functions including emotional processing, stress regulation, but also in learning tasks and memory formation [66-69]. Furthermore, the maturation and formation of new neurons within the hippocampus has been shown to be critical for normal hippocampal function [70,71] and the disturbances seen in the mouse model could be the explanation for the displayed smaller hippocampus. Reduced hippocampal volumes are commonly observed in several neuropsychiatric disorders including post-traumatic stress disorder [72], schizophrenia [73,74], and major depressive disorder [75,76].

So even though it is likely that CYP2C19 enzymatic activity affects fetal brain development, a hippocampal and behavioral phenotype does not fully develop until young adulthood in the transgenic mice, similar to major depressive disorder and other neuropsychiatric disorders in humans were the manifestation generally occurs at this age [77,78]. A role of CYP2C19 in the metabolism of endogenous substances during brain development seems to be a likely explanation for the phenotypes observed in the transgenic mouse model but the identities of these substances remain to be discovered. The *CYP2C19* transgenic mouse model indeed suggests that this enzyme is involved in the transformation of endogenous substrates involved in important brain developmental processes. These data are interesting and in line with the previously described link between the *CYP2C19* polymorphism and depressive symptoms. One can speculate that the CYP2C19 phenotypes poor and rapid metabolizers have dissimilarities in their brain functions due to the presence of different levels of CYP2C19 during human brain development. Studies focused on this aspect in the developing human brain would be of severe interest in the future.

Conclusions

Psychotropic drug metabolizing enzymes, including cytochrome P450s, are present in the brain [79,80] where they not only could contribute to local drug metabolism but also affect local biochemical homeostasis. CYPs, especially CYP2D6 and CYP2C19, are suggested to be involved in the transformation and metabolism of many endogenous substances including neurotransmitters and neurosteroids. Liver and brain levels of CYPs are highly dependent on genetic polymorphism which causes interindividual differences in drug levels and response. However, interindividual differences in local brain expression of these enzymes might also explain the reported associations between genetic polymorphism of e.g. *CYP2D6* and *CYP2C19* and personality traits, affective behaviour, and vulnerability to neuropsychiatric disorders as summarized in Table 2. This might raise some ethical issues with regard to the genetic tests recommended to determine treatment outcome and dose adjustments of many drugs metabolized by theses enzymes. However at the present stage such links are still not evidently shown and more research is needed before we can conclude that this would constitute an issue.

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