Editorial
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Pharmacogenomics

Polymorphic expression of CYP2C19 and CYP2D6 in the developing and adult human brain causing variability in cognition, risk for depression and suicide: the search for the endogenous substrates

"Although these polymorphisms are not causing an apparent phenotype, accumulating evidence indicates that they can influence brain function."

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Introduction

The two major cytochrome P450 polymorphisms, with respect to variable drug response, are those of *CYP2C19* and *CYP2D6*. Both gene variations can cause abolished, reduced, normal or increased enzyme expression translating into the poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizer phenotypes [1]. Multiple gene copies of *CYP2D6* emerged in Ethiopia and North Africa in order to make the inactivation of the toxic plant alkaloids this enzyme metabolizes more efficient [2]; evaluation of the Neanderthal sequences reveals defect CYP genes [3]; these data indicate a long history of polymorphism in these genes. Although these polymorphisms are not causing an apparent phenotype, accumulating evidence indicates that they can influence brain function.

CYP2D6 in the brain

CYP2D6 has been found in neurons in numerous human brain areas, including the thalamus, hypothalamus, hippocampus, substantia nigra, cerebellum, and in several layers of the frontal neocortex [4,5] raising questions about its potential role in these neurons. The enzyme was implicated in metabolism of the endogenous compounds 5-methoxytryptamine, anandamide, progesterone and tyramine and in generation of serotonin and dopamine from trace amines [6].

This hypothesis is strengthened by the fact that in a transgenic mouse model, with *CYP2D6* expressed in the brain, higher serotonin levels have been measured in several brain regions, including the cerebellum and hippocampus [7]. CYP2D6 might also affect the endocannabinoid system within the CNS due to its ability to metabolize anandamide and its derivatives [8]; however, the physiological significance of such metabolism is still unclear.

CYP2D6 & brain phenotypes

Associations between *CYP2D6* genotypes and personality traits gave 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 PMs displayed higher impulsivity-related traits [9], which was confirmed by a later study [10]. Others have found PMs to be more anxiety-prone and less successful in socialization when compared with EMs [11,12]. These heterogeneous results might be related to different ethnicities of the subjects and different methods used for monitoring the personality, but do suggest that CYP2D6 might have an endogenous role in the human brain influencing behavior.

The UM CYP2D6 phenotype has been suggested to predict suicidal risk [13,14] and increased suicidal behavior among individu-

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als with eating disorders [15]. In search for a physiological effect of higher *CYP2D6* brain expression in such individuals, Stingl and collaborators examined the perfusion rates in the thalamus and the right hippocampus among healthy human subjects. They detected an effect of *CYP2D6* polymorphism on resting-state perfusion in the thalamus, hypothalamus, posterior cerebral cortex, and isolated parts of the medial temporal lobe and orbitofrontal cortex, where PMs had lower perfusion rates, a pattern that suggested an association with brain circuits involved in vigilance. Also, they tested the effect of the *CYP2D6* polymorphism on a standard working-memory task and recognition of facial expressions, a task eliciting neural circuits related with the detection of emotionally arousing stimuli measured with fMRI. In both studies they found an effect of the *CYP2D6* polymorphism in visual areas in the posterior cerebral cortex, whereas no effect could be detected in areas outside of those staked out by the previous perfusion study (see [16] and references therein). This provides an interesting mechanistic link to the findings concerning a relationship to suicide.

CYP2C19 expression in the developmental brain

Expression of *CYP2C19* in humans has long been thought to be restricted to the liver and small intestine [1]; however, using a transgenic mouse model with 12 gene copies of the *CYP2C19* gene it was shown that the human *CYP2C19* gene is expressed in fetal brain and silenced completely 1 week after birth [17]. Analyses of human fetal brain samples showed relatively high cortical expression levels of *CYP2C19*, around 0.5% of that seen in adult liver [17]. Altogether, these data indicate a transient fetal brain expression of *CYP2C19* that might affect development.

Like CYP2D6, CYP2C19 has broad substrate specificity and it metabolizes many different classes of psychotropic drugs, including selective serotonin-reuptake inhibitors, tricyclic antidepressants such as amitriptyline, benzodiazepines such as diazepam, and the anticonvulsant drug mephenytoin [1].

CYP2C19 & brain phenotypes

CYP2C19 polymorphism was associated with depressive mode in humans in study encompassing 1742 twins. Twins carrying allelic variants causing high activity of the enzyme (*CYP2C19*1*) showed more depressive symptoms than the subjects carrying a defective allelic variant (*CYP2C19*2*), based on their significantly lower T1 scores in the center for epidemiologic studies depression (CES-D) scale and lower scores on the subscales depressed mood, psychomotor retardation, and somatic complaints, compared with extensive metabolizers [18].

The effect of the *CYP2C19* genotypes on brain function and morphology was studied in the *CYP2C19* transgenic mice. As adults they showed decreased hippocampal volume, an anxious phenotype, and increased hippocampal activation after acute stress [17]. The reduction in the hippocampal volume appears to be directly caused by *CYP2C19* expression; the homozygotes were showing a more dramatic reduction of hippocampal volume [60%] than hemizygotes [12%] after birth. Reduced hippocampal volumes are commonly observed in several neuropsychiatric disorders including post-traumatic stress disorder, schizophrenia, and major depression (see [17] and references therein).

Adult *CYP2C19* hemizygotes showed increased stress sensitivity and increased anxiety-like behavior. Stressful life events and stress sensitivity are major risk factors for psychiatric diseases making this animal a model of interest for factors involved in the regulation of stress response. These mice also showed a reduced number of GABAergic interneurons in the dentate gyrus of the hippocampus, the region in which $\alpha 2GABA_A$ and not $\alpha 3GABA_A$ receptors are present [19]. Anxiolytic effects of benzodiazepines are mediated by $GABA_A$ receptor subtypes containing $\alpha 2$ and $\alpha 3$ subunits [20]; therefore, it might be plausible that the reduced number of GABAergic interneurons in the dentate gyrus leads to hippocampus over-activation in stress and the anxious mouse phenotype by decreasing hippocampal $\alpha 2GABA_A$ signaling.

CYP2C19 has been shown to metabolize cannabinoid compounds [21], previously shown to be important for the successful migration of GABAergic neurons to the hippocampus [22]. During hippocampal development, CB1 is present in GABA interneurons [23]; therefore, it can be hypothesized that the reduced number of GABA interneurons observed in *CYP2C19* transgenic mice is caused by impaired cannabinoid signaling in developing hippocampus.

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; however, the identities of these substances remain to be discovered.

Synergy of increased CYP2C19 & CYP2D6 activity

CYP2D6 and CYP2C19 have to a great extent overlapping substrate specificities. A recent study by Llerena and collaborators examining suicide risk among subjects having both high *CYP2D6* and *CYP2C19* expression is interesting [24]. Thus, patients with a high CYP2D6-CYP2C19 metabolic capacity showed an increased risk for a severe suicide attempt as measured

by the SIS-objective circumstance subscale, particularly in absence of a family history of suicide. Those with no family history of suicide are less vulnerable and consequently may need more stressful triggers to precipitate it, indicating that having a higher CYP2D6-CYP2C19 metabolic capacity can be associated with the increased sensitivity to these triggers.

Conclusion

Increasing evidence suggest that the polymorphic enzymes CYP2C19 and CYP2D6 indeed have endogenous functions in the development and regulation of specific neuronal pathways, translating into inter-individual differences in cognition and risk for depression and suicide. Enzyme-coding gene polymorphisms determine metabolic rates of a large number of psychotropic drugs modifying their concentrations at the site of action and can predict a need for adjustments in dosage. Since the enzymes also metabolize endogenous psychotropic substances, it is very likely that the observed brain phenotypes involve their altered metabolism at different stages of brain development and during adulthood. Although being a difficult task, the identification of these compounds would provide an important knowledge for the molecular and cellular control of phenotypic alterations and lay a ground for possible future pharmacologic interventions.

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