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Review

Xenobiotic metabolizing enzymes in the central nervous system: Contribution of cytochrome P450 enzymes in normal and pathological human brain

Fabien Dutheil [a], Philippe Beaune [a,b], Marie-Anne Loriot [a,b,*]

[a] *Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S775, Université Paris Descartes, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France*

[b] *Assistance-Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Biochimie, Pharmacogénétique et Oncologie Moléculaire, 20 rue Leblanc, 75908 Paris Cedex 15, France*

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Abstract

The metabolism of xenobiotics in human brain constitutes a field of recent intensive research in relation to the potential implications in the pharmacological effect of drugs acting on the central nervous system. Cytochrome P450 enzymes (CYPs) play a crucial role in these metabolic pathways and the existence of functional CYP monooxygenases in brain is now well established. These enzymes are preferentially localized in the neuronal cells within the microsomal fraction and the inner membrane of mitochondria. Although low, the metabolism *in situ* could influence individual response to xenobiotics or produce reactive, toxic metabolites causing irreversible damage in the neuronal cells. The abundant presence of CYPs in selective cell populations within different regions of the brain has also suggested a role for these enzymes in brain physiology thus not restricted to xenobiotic-induced neurotoxicity. For instance, CYPs participate in the regulation of neurotransmitters and steroids and brain maintenance of cholesterol homeostasis. Recent advances support an additional role for these enzymes in the pathogenesis of psychiatric and neurodegenerative disorders such as depression, schizophrenia, and Alzheimer's and Parkinson's diseases. The characterization of brain CYP isoforms and their localization, the identification of their substrates and metabolic end-products will allow better understanding of the role of these enzymes in brain physiology, development and diseases.

Keywords: Cytochrome P450 enzymes; Human brain; Xenobiotics; Endogenous substrates; Neurodegenerative diseases

1. Introduction

Xenobiotics are low molecular weight (below ≈1000 Da) chemical compounds foreign to the body. They are found in all compartments of our environment (air, food, etc.) and whether or not exposure is deliberate (e.g. drugs) or involuntary (e.g. pollutants), it is nevertheless unavoidable. Metabolism of foreign compounds to polar hydrophilic metabolites is an important prerequisite for detoxification and elimination of xenobiotics from the body; although, in general, it results in detoxification but in some cases, xenobiotics can be bioactivate into reactive toxic intermediates that may cause toxicity [1,2]. Since the body is not familiar with the chemical natures of the great variety of possible xenobiotics, it must have available a wide range of different enzyme activities that can catalyze a huge panoply of chemical reactions, including isoenzymes which can recognize diverse chemical structures. Among them, cytochrome P450 enzymes (CYPs) play a crucial role and constitute a superfamily of enzymes involved in the oxidative metabolism of both endogenous and exogenous substrates.

* Corresponding author. Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S775, Université Paris Descartes, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France. Tel.: +33 (0)1 42 86 22 51; fax: +33 (0)1 42 86 20 72.
E-mail address: marie-anne.loriot@univ-paris5.fr (M.-A. Loriot).

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Liver is the main location of xenobiotic metabolism. However, extra-hepatic sites of xenobiotic metabolism including the gut, lung are now clearly established, and the pharmacological and toxicological consequences of *in situ* metabolism have been recognized in humans and in animals [3]. The identification of CYPs in brain within specific cell types, particularly in the neuronal cells, raises the question of the possible specific functions of these enzymes in brain physiology. The presence of CYPs should be important in inducing a bioactivation and cellular damage in this target organ for both centrally active drugs and environmental toxics crossing the brain-blood barrier. Because of their lipophilic character xenobiotics can diffuse through the blood–brain barrier to enter the neuronal cells. According to the limited capability to regeneration of these cells, the brain is thus highly vulnerable to damage by toxic compounds.

In this review we will focus on the nature and the distribution of the isoforms of CYPs in the human brain, and on the recent understanding of the role of these enzymes in brain physiology as well as in response to xenobiotics (drugs, toxic compounds) and in the pathogenesis of neurodegenerative disorders.

2. Cytochrome P450 enzymes in brain

The CYP brain content first evaluated in rat from microsomal preparations was of 30 pmol/mg of protein, which is approximately 3% of the corresponding level in the liver [4]. However the enzymes are not uniformly distributed among the different regions and cells of the brain and sex-related differences have also been reported. In the human brain, the CYP content reaches up to 100 pmol/mg of microsomal protein, which is 10% of the corresponding level in the liver microsomes [5]. For other authors, brain CYP quantity accounts for only 1–5% of liver CYPs [6]. Moreover, cytoarchitectonic organization and cell functions are extremely variable in brain and, when compared cell to cell, the levels of CYPs in specific neurons can be as important or more so than levels in hepatocytes [7]. Differential expression according to the cerebral region has been described, with the highest CYP content in the brain stem and cerebellum and the lowest values in the striatum and hippocampus, showing some degree of similarity with rat brain [8,9]. Every CYP isoform is also distributed among different regions with a specific expression pattern. For example, CYP1B1 was mainly found in putamen, spinal cord, medulla oblongata, frontal and temporal cortex and to a lower extent in cerebellum, hippocampus, thalamus and amygdala; this isoform was very weakly detected in substantia nigra [10]. CYP2D6 protein is mainly present in substantia nigra, caudate nucleus and entorhinal cortex and to a lesser extent in putamen, cerebellum, hippocampus, and globus pallidus [11]. The CYP subcellular localization in brain is extremely diverse. In the liver, CYPs are primarily located in the endoplasmic reticulum or microsomal cell fraction, whereas in the brain, CYPs are found in the endoplasmic reticulum fraction, the inner membrane of the mitochondria. It is now established that brain CYPs correspond to the functional enzymatic system. Thus, it has been shown that these enzymes metabolize xenobiotics such as dextromethorphan and amitriptyline as well as endobiotics like arachidonic acid [12,13]. In the brain, CYP activity was found in both microsomal and mitochondrial subcellular fractions [14].

2.1. Location of the main human CYP isoforms

Human CYPs that are present in brain are listed in Table 1. To date, 41 of the 57 human CYPs have been identified in brain, and among them, 20 isoforms (CYP1A1, 1A2, 1B1, 2B6, 2C8, 2D6, 2E1, 3A4, 3A5, 8A1, 11A1, 11B1, 11B2, 17A1, 19A1, 21A2, 26A1, 26B1, 27B1 and 46A1) were found in several brain localizations. Moreover, a limited number of CYP isoforms have been extensively studied in human brain: CYP1A1, 1A2, 2B6, 2D6, 2E1 and 46Al; most of these are largely distributed in brain regions (e.g. cortex, cerebellum, basal ganglia, hippocampus, substantia nigra, medulla oblongata, pons), but data vary depending on the reports (Table 1). The discrepancies between the studies are likely due to the different techniques used in order to identify the presence of CYPs in brain. The techniques used for detection of mRNA comprise real-time PCR, RT–PCR, Northern blot, Southern blot, RNA dot blot, FISH and *in situ* hybridization for mRNA or cDNA detection, while Western blot and immunostaining are used for protein detection. The conflicting results between studies are partly explained by the problems of specificity and sensitivity of primers or antibodies due to the high degree of sequence homology between CYPs [15].

Brain regions differ in cell types, density and function and the expression pattern of brain CYPs is also extremely variable [16]. CYP1A1 was predominantly localized in neurons of cerebral cortex, Purkinje cells and granule cell in dentate gyrus and pyramidal neurons of CA1, CA2 and CA3 subfields of hippocampus and reticular neurons in midbrain [17]. It has also been found in basal ganglia [18]. CYP1A2 mRNA has been found in most of the brain regions examined [19]. CYP1A1, CYP1A2, CYP2A6 and CYP2E1 were detected in the mitochondria of different brain regions such as striatum, thalamus, pons and medulla oblongata [20]. CYP1B1 was strongly expressed in the nuclei of a majority of astrocytes and neurons in human brain cortex [21]. CYP2B6 is also largely distributed in brain but the basal level of expression is generally low [22]. In the neocortical layer I, this enzyme is present in both neurons and glial cells, including astrocytes surrounding cerebral blood vessels where this CYP colocalizes with glial fibrillary acidic protein [23]. CYP2D6 is the most extensively studied enzyme because early on it was found to be associated with personality traits [24] and in neurological disorders such as Parkinson's disease [25]. Immunoblot studies revealed the presence of CYP2D6 in cortex, cerebellum, midbrain, striatum and thalamus [26]. Immunohistochemical localization showed the predominant presence of CYP2D6 not only in neuronal soma but also in dendrites of Purkinje and cortical neurons [26]. Just as for human CYP1A1, 1A2, 2B6 and 2D6, CYP2E1 protein is found in a number of brain regions