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COMMENTARY

Metabolism of Xenobiotics in the Central Nervous System

IMPLICATIONS AND CHALLENGES

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ABSTRACT. The metabolism of drugs and other xenobiotics *in situ* in the brain has far-reaching implications in the pharmacological and pharmacodynamic effects of drugs acting on the CNS, particularly with respect to psychoactive drugs wherein a wide range of therapeutic response is typically seen in the patient population. An entirely functional cytochrome P450 (P450) monooxygenase system is known to exist in the rodent and human brain, wherein it is preferentially localized in the neuronal cells, which are the sites of action of psychoactive drugs. Further, bioactivation of xenobiotics, *in situ*, in the CNS would result in the formation of reactive, toxic metabolites in the neuronal cells that have limited regenerative capability. The presence of P450 enzymes in selective cell populations within distinctive regions of the brain that are affected in certain neurodegenerative disorders implies the potential role of P450-mediated bioactivation as a causative factor in the etiopathogenesis of these diseases. The characterization of brain-specific P450s and their regulation and localization within the CNS assume importance for understanding the potential role of these enzymes in the pathogenesis of neurodegenerative disorders and psychopharmacological modulation of drugs acting on the CNS. BIOCHEM PHARMACOL **56**;5:547–551, 1998. © 1998 Elsevier Science Inc.

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Metabolism of foreign compounds in the body to polar, hydrophilic metabolites is an important prerequisite for detoxification and elimination of xenobiotics from the body. A major family of enzymes involved in the metabolism of foreign compounds is P450† and associated monooxygenases. Multiple forms of P450 that are selectively induced or inhibited by a variety of drugs are known to exist in the liver, the major organ involved in P450-mediated metabolism [1]. In recent years, the extent of P450-mediated metabolism in extrahepatic organs (such as lung, kidney, skin, and nasal epithelium) and the pharmacological and toxicological consequences of *in situ* metabolism in target organs have been recognized in laboratory animals [2] and humans [3]. These studies have revealed the preferential localization of drug-metabolizing enzymes within specific cell types in these organs, rendering them vulnerable to damage by bioactivation *in situ* within these cells.

The brain, particularly the human brain, is perhaps one of the most complex organs, both functionally and anatomically. The brain exhibits a multitude of diversity, both with respect to its distinct anatomical regions and its cellular elements. I would go so far as to state that it is inappropriate to consider the brain as a single organ; it is a collection of anatomically distinct entities, each with its specialized function, which are interconnected through a complex neural network for effective communication. The brain is highly vulnerable to damage by toxic compounds, due to the limited regenerative capability of the neurons, the major cell type involved in neurotransmission and other specialized functions of the brain. The distinctive features of the capillary endothelial cells surrounding the cerebral blood vessels render protection to the brain by preventing the entry of circulating molecules. The blood–brain barrier, as this hypothetical barrier is commonly known, results from the presence of tight junctions and the paucity of pinocytotic vesicles. However, xenobiotics that are lipophilic in character can diffuse through the endothelial cells of the brain capillaries and enter the neuronal cells. Thus, bioactivation *in situ* in the neuronal cell can have far-reaching consequences by causing irreversible disruption of neuronal function. The brain is the target not only for a number of toxic compounds but also for several psychoactive drugs. The metabolism of drugs in the brain can lead to local pharmacological modulation at the site of action and can result in variable drug response.

One of the major groups of diseases that affect the brain is mental disorders. Mental disorders (psychiatric disorders)

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† *Abbreviations:* P450, cytochrome P450; EM, extensive metabolizer; PM, poor metabolizer; and RT/PCR, reverse transcriptase/polymerase chain reaction.

comprise a group of diseases including affective disorders (such as depression and bipolar disorders) and schizophrenia, which affect a large segment of the population. In recent years, the focus of research in psychiatry has shifted from the mind to the brain, as new and exciting scientific advances have been made in basic neuroscience. Thus, the biological basis of mental disorders has been firmly established, and the treatment of major psychiatric disorders has become more pharmacologic and less psychotherapeutic. However, a considerable segment of the patient population (20–30%) does not show significant clinical improvement. Plasma drug levels, which are often used as indicators of bio-availability of a drug, reflect the variability in hepatic drug metabolism. Nevertheless, it is being increasingly recognized that a significant number of patients with adequate plasma levels do not respond to psychoactive drugs, and patients with acceptable plasma levels of drugs exhibit toxic side-effects due to the drugs. Thus, plasma levels of drugs are not always effective indicators of therapeutic outcome [4]. The rate of drug metabolism in a typical population is known to vary significantly from person to person (inter-individual variation); therefore, metabolism occurring at the site of action could amplify these variations and result in tremendous differences in the drug response among the patient population, as we often see among psychiatric patients. Thus, if the drug *per se* is the active ingredient, faster metabolism of the drug in the brain could lead to rapid loss of pharmacological action. On the other hand, if the metabolite were the pharmacologically active entity, faster metabolism of the drug could lead to a high concentration of the active species in the brain. In fact, since the side-effects are typically related to the rate of metabolism of the drug, the range of side-effects (often involving the CNS) seen in patients could be potentially attributed to the differences in their capability to metabolize drugs at the site of action, namely, the brain. An understanding of drug metabolism in the brain is therefore essential for the development of both new drugs and better therapeutic strategies for existing drugs.

Psychoactive drugs, such as antidepressants and neuroleptics, are metabolized by hepatic P450. The specific forms of hepatic P450 involved in the metabolism of some of these drugs have been characterized in both rat and human liver [5, 6]. The major forms of P450 that have been demonstrated to play a predominant role in the metabolism of psychoactive drugs in both rat and human liver belong to the P4503A, 2D, 2C, and 1A families. P4502D6 is a constitutive form of hepatic P450, identifiable in rat and human liver where it mediates the hydroxylation of imipramine, amitriptyline, and chlorimipramine.

Several psychoactive drugs modulate (inhibit or induce) hepatic P450 levels. The specific serotonin reuptake inhibitors fluoxetine and its metabolite norfluoxetine are potent inhibitors of P4502D6, and the concentrations of imipramine and nortriptyline increase five-fold when co-administered with fluoxetine [7]. The neuroleptic haloperidol is also a potent inhibitor of P4502D6 [8]. However, imipramine, an antidepressant, induces P450 levels in liver. Further, co-administration of imipramine with chlorpromazine induces hepatic P450 to a greater extent than imipramine alone [9]. The effect of these drugs on brain P450 remains largely unknown. Since psychoactive drugs are typically administered for relatively long periods of time and often as part of a multiple drug regimen, chronic effects of these drugs on the xenobiotic-metabolizing capability of the brain is a matter of concern.

The hepatic metabolism of these drugs by P450-associated monooxygenases and the genetic polymorphism exhibited by some forms of P450 (e.g. 2C and 2D6) are generally understood [5]. These variables are reflected in the plasma levels of the administered drugs. Thus, the PM phenotypes of P4502D6 often exhibit higher plasma drug levels and slower elimination rates [10]. But the plasma drug level often shows poor correlation with the therapeutic effect. For example, poor correlations are often observed between blood levels of neuroleptics and antidepressants and their therapeutic effects [11], suggesting that metabolism within the brain could influence the therapeutic outcome, regardless of the hepatic clearance and plasma drug levels.

Hydroxylation of drugs by P450 results in the formation of hydrophilic metabolites that can be excreted easily by the kidney. However, if such hydroxylated metabolites were to be formed in the brain, it would result in the prolonged presence of the metabolite and lower clearance from the brain.

Minor metabolic pathways of drugs that are not of significance in the liver could potentially produce significant pharmacological responses, if they were to occur at the site of action within specific nuclei in the brain. Morphine, the O-demethylated metabolite of codeine, is a powerful analgesic, whereas codeine is very much less active. The major pathways for the metabolism of codeine are P450-mediated N-demethylation and glucuronidation. A minor metabolic pathway catalyzed by P4502D6 is the O-demethylation of codeine, resulting in the formation of morphine [12, 13]. It is debatable whether significant amounts of morphine are formed in the liver to account for the analgesic effect of codeine. However, even if a very small amount of codeine were to be metabolized to morphine close to or at the site of action, which is the brain, it could possibly account for the analgesic effect of codeine. It has been shown that codeine is metabolized to morphine in the brain [14]. More interestingly, it has also been observed that the pain threshold is elevated in the EM phenotype but not in the PM phenotype after administration of codeine, suggesting the metabolism of codeine to morphine at the site of action [15].

A moderate difference in the pharmacokinetics of psychoactive drugs often leads to dramatic pharmacodynamic effects, again suggesting that metabolism at the site of action could play a significant role. An example of such an effect has been described by Brosen and coworkers [16]. The total plasma clearance of remoxipride is two times higher in

EMs than in PMs, suggesting that it may be metabolized in part by P4502D6. However, in a recent clinical study, sixteen subjects who were EMs were treated with remoxipride (100 mg, twice daily for 3 days), and no adverse effects were observed. However, at the same dose all four PM subjects developed severe side-effects (acute dystonia and acathesia) and had to be dropped from the study. Although the plasma clearance between PMs and EMs differed only two-fold (pharmacokinetic difference), the pharmacodynamics showed dramatic effects, indicating that differences in metabolism of the drug at the site of action could be responsible for these effects.

This raises the question of whether the brain can metabolize xenobiotics? What is the P450 content in the brain and where is the enzyme localized? The quantitation of microsomal P450 in the brain was first attempted in 1977 by Sasame and coworkers [17], who reported that the P450 content in rat brain was 30 pmol/mg of protein, which is approximately 3% of the corresponding level in liver. More recently, we found that isolation of brain microsomes under more stringent conditions results in a higher recovery of P450 (100 pmol/mg of protein), that is 10% of the corresponding hepatic levels [18]. However, the enzyme is not uniformly distributed among the different regions of the brain, and some of the highest P450 levels have been detected in olfactory lobes, cerebellum, and brain stem [19–21]. We find that in the brainstem and cerebellum P450 levels are 150 and 140 pmol/mg of protein, respectively, which are about 15% of the corresponding hepatic levels [21]. A sex-related difference also has been observed in total P450 in both mouse and rat brain. The P450 content in the female rat brain (50–60 pmol/mg of protein), as reported by us [22] and others [23], is significantly lower than the corresponding levels in male rat brain (80–100 pmol/mg of protein). Brain P450 is regulated by sex hormones, and the administration of testosterone to immature female rats increases P450 levels to that observed in male rats [24]. It is not known whether P450 is similarly regulated in the human brain; if this were so, it raises the possibility that pharmacodynamics of psychoactive drugs in the brain might differ substantially between males and females. We do have evidence that a substantial amount of P450 is present in the human brain. P450 content [25] and associated monooxygenase activities [26] have been measured in microsomes from human brain tissue obtained at autopsy. Regional differences have been noted in the distribution of P450 in human brain; the hemeprotein levels are highest in the brain stem and cerebellum and lowest in the striatum and hippocampus [25], showing some degree of similarity with the observations made in rat brain.

The microsomal P450 systems in both rat and human brains are entirely functional and are capable of metabolizing a variety of classical substrates for P450 [27–30]. Multiple forms of P450 (such as 1A1, 1A2, 2B1, 2B2, 2E1, 3A, and 2D) that catalyze the oxidation of various substrates are constitutively expressed in rat brain as demonstrated by RT/PCR and immunoblotting experiments [31–38]. These multiple forms of P450 are selectively inducible by administration of β-napthoflavone [39], phenobarbital [34], and 3-methylcholanthrene [34, 40]. Studies from our laboratory have also shown that administration of ethanol chronically for 1 month to male rats results in the induction of rat brain P450 levels [28]. Administration of nicotine, interestingly, results in selective induction of brain P450 in certain regions, whereas hepatic P450 levels are unaffected [20]. This apparently preferential effect of nicotine on brain P450 may be of particular significance as it indicates the possible regulation of brain P450 by mechanisms independent of and different from those known for hepatic P450s.

A certain amount of inconsistency is apparent upon review of the available information on the presence of various forms of P450 in the brain (as detected immunologically or by mRNA analyses). Immunological studies have been carried out by various laboratories with polyclonal or monoclonal antibodies, which certainly contributed to variability in the observations reported. Similarly, the RT/PCR studies have been performed using a variety of oligonucleotide primers, undoubtedly lending a certain variability to the results. The limited homology between brain and liver P450 could further account for the divergence of experimental results. The more detailed future characterization of individual forms of brain P450 therefore assumes greater importance. An effort in this direction by Strobel and coworkers [41] has resulted in the cloning and expression of a brain-specific P450 designated P4502D18, which is involved in the N-demethylation of the antidepressant imipramine. This is the first demonstration of the involvement of a brain-specific P450 in the biotransformation of a psychoactive drug.

Based upon the immunological similarity observed between the multiple forms of hepatic and brain P450s by immunoblot analyses, immunocytochemical localization studies of brain P450 have been pursued with antisera to the corresponding hepatic forms of P450. In our laboratory, immunohistochemistry of rat brain P450 was attempted using an antiserum to purified rat liver P450(2B1/B2) [34], which demonstrated the predominant localization of the enzyme in the neuronal cell body, especially in the reticular formation and lower cranial nerve nuclei of the medulla oblongata. Similarly, an antiserum to a phenytoin-inducible form of P450 also revealed P450 in neuronal cell bodies [42]. The preferential localization of P450 in the neuronal cells within the brain, as observed by immunohistochemistry, also has been confirmed by measurement of P450-associated monooxygenases in freshly isolated neurons and glia. In freshly isolated cells, P450-associated monooxygenase activity was higher in the neuronal cells than in the glial cells [43]. Taken together, these observations suggest the predominant presence of P450 in the neuronal cells, which are, incidentally, the sites of action of psychoactive drugs.

The presence of P450 in neuronal cells, which have very limited regenerative capability, brings forth the potential consequences of bioactivation of xenobiotics *in situ* in the

CNS. A group of brain-related disorders that are of immediate concern is the neurodegenerative diseases, so-called because of the progressive and irreversible nature of the diseases in this category. The diseases categorized under this group include, among others, Parkinson's disease, Alzheimer's disease and motor neuron disease (also known as amyotrophic lateral sclerosis). In each of these diseases, specific cell populations within specialized regions of the brain are affected, leading to the selective loss of function. A major challenge facing neuroscientists today is the identification of molecular mechanisms involved in the pathogenesis and progression of these neurodegenerative disorders in order to develop better prophylactic and therapeutic strategies. While the involvement of genetic factors is recognized in the familial forms of the diseases, the biochemical mechanisms involved in the pathogenesis of the sporadic forms of these diseases (which make up more than 90% of the observed cases) remain largely unknown. More recently, a role for environmental toxicants has been postulated in the pathogenesis of these disorders. The above hypothesis has gained ground following the incidence of Parkinson's disease in young adults exposed to a synthetic heroin substitute. The neurotoxicant involved, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (commonly known as MPTP), was detected to be a contaminant, formed in small amounts as a by-product during the synthesis of the designer drug. MPTP, by itself, is not neurotoxic, but is metabolized in the brain to a toxic compound, 1-methyl-4-phenylpyridinium (MPP^+), through the enzyme monoamine oxidase (which is primarily involved in the catabolism of neurotransmitters like dopamine, serotonin, and norepinephrine). MPP^+ is then accumulated into specific neurons in selected regions of the brain through the dopamine transporter [44]. Thus, exposure to MPTP causes selective loss of function in the extrapyramidal tract of the brain, leading to a movement disorder very similar to Parkinson's disease. The discovery that exposure to a synthetic chemical could potentially cause a neurodegenerative disease akin to that seen in humans has provided the necessary impetus to look at the role of exogenous toxins in the pathogenesis of neurodegenerative disorders. The specialized features of the nervous system, like the neurotransmitter transporters, can help concentrate certain xenobiotics in specific cell types within the nervous system. The observations made with MPTP have demonstrated how the unique features of the CNS can potentially help bioactivation of inert compounds to ultimate toxins, help in their sequestration in target cells, and cause irreversible damage to specific regions of the brain, thus bringing about selective loss in function. The localization of P450 in specific cell types within CNS regions that are selectively affected in certain neurodegenerative disorders, such as its presence in the anterior horn cells of the spinal cord [45], which are selectively damaged in amyotrophic lateral sclerosis, or in the neurons of substantia nigra, which are affected in Parkinson's disease, indicates the possible role of P450-mediated bioactivation of xenobiotics within these cells as a causative factor. However, definitive evidence is lacking.

The potential roles of brain P450s in pharmacological modulation of drugs acting on the CNS and *in situ* bioactivation of xenobiotics in the CNS are apparent. However, our knowledge of brain-specific P450s, particularly the human brain enzymes, their regulation and specific localization is rather meager [46]. The heterogeneity and complexity of the CNS pose a particular challenge since multiple forms of P450 are distributed and regulated differentially in distinctive regions of the brain. A multidisciplinary approach involving biochemical, morphological, and molecular biological investigations may provide some answers.

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