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Cytochromes P450 in the brain: Emerging evidence for biological significance

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Abstract

Cytochrome P450 (CYPs) enzymes are responsible for the metabolism of many exogenous and endogenous compounds. CYPs are abundant in the liver and are also expressed in many extra-hepatic tissues including the brain. Although the total CYP levels in the brain are much lower than in the liver, brain CYPs are concentrated near drug targets in specific regions and cell types, potentially having a considerable impact on local metabolism. Individual differences in brain CYP metabolism, due to inducers, inhibitors or genetic variation, can influence sensitivity and response to centrally acting drugs. Brain CYPs may also play a role in modulating brain activity, behavior, susceptibility to CNS diseases and treatment outcomes. This review highlights the recent progress that has been made in understanding the functional significance of CYPs in the brain.

Cytochrome P450 enzymes in the brain

Cytochromes P450 (CYPs) are a super family of enzymes that are important in metabolizing a vast array of compounds, including clinically used drugs, drugs of abuse, toxins and endogenous molecules. CYPs are expressed in the liver and other organs, including the brain, where they can contribute significantly to local metabolism [1]. Here we discuss recent findings related to the expression, activity and regulation of CYPs in the brain; the role of brain CYPs in modulating sensitivity to exogenous and endogenous compounds; and the potential impact of brain CYPs on behavior, disease pathology and treatment outcomes. We focus on drug metabolizing CYPs, most of which belong to CYP families 1–4.

Expression and activity of CYPs in the brain

CYPs have been detected in the brains of multiple species including rat, mouse, dog, monkey and human [2] (Table 1). In general, the distribution of drug metabolizing CYPs in the brain is heterogeneous, with expression levels varying among different brain regions. For example, in the human brain, CYP2B6 protein expression varies significantly among brain regions with a 2.5-fold range [3] (Figure 1a). Within a particular brain region, CYP expression is usually restricted to specific populations of neurons and/or glia. In the frontal cortex of the human brain, CYP2B6 is highly expressed in astrocytes surrounding cerebral blood vessels in layer I, whereas CYP2D6 can be found predominantly in pyramidal neurons in layers III–V and also in white matter [3, 4]. In the cerebellum of human non-smokers, CYP2B6 and CYP2D6 are expressed in neurons within the molecular and granular layers, but are undetectable in Purkinje cells; however in human smokers, CYP2B6 and CYP2D6 are highly expressed in the Purkinje cells of the cerebellum [3, 5] (Figure 1b and 1c). The region- and cell-specific expression of CYPs in the brain may provide some insight into their functional significance and metabolic roles. For instance, the high expression of

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CYP2B6 at the blood-brain interface may help to regulate the penetration of drugs and toxins into the brain [2].

Total CYP levels in the brain are low, approximately 0.5–2% of that in the liver, making it unlikely that CYP-mediated metabolism in the brain substantially influences systemic metabolite levels [1]. However, the localization of brain CYPs to specific regions and cell types allows for a potentially considerable impact on metabolism in certain brain microenvironments and the brain as a whole [6]. The levels of CYPs in specific neurons may be comparable to, or even higher than levels in hepatocytes. For example, nicotine-induced CYP2B expression in neurons within the rat frontal cortex, when processed in the same conditions as liver slices, appeared to exceed levels found in hepatocytes [7].

There are sex-based differences in the expression of some hepatic CYPs (see Ref [1] for review). Only a few studies have investigated sex differences in the expression of CYPs in the brain, several of which assessed CYP19, which metabolically converts androgens to estrogens [8]. Male rats exhibit higher CYP19 activity in certain brain regions, such as the hypothalamus, compared to females [9], however sex differences in the expression of CYP19 were not observed in the adult human brain [10].

In vitro brain and liver CYPs are capable of metabolizing the same broad range of endogenous and exogenous compounds [1] (Table 1). Although these *in vitro* studies suggest a role for CYP-mediated metabolism in the brain, until recently it was unclear whether conditions in the brain, such as levels of endogenous heme and the concentration of necessary co-factors and co-enzymes, were sufficient to support CYP activity *in vivo* [2]. The demonstration of brain CYP function *in vivo* is challenging due to the presence of substantial hepatic metabolism, which generates metabolites that can enter the brain from the periphery. However recently a novel approach, in which a radiolabeled, mechanism-based irreversible CYP2B6 inhibitor was delivered directly into the brain, was used to demonstrate the metabolic activity of basal and induced brain CYPs *in situ* [11] (Figure 2). Radiolabeled ^{3}H-8-methoxypsoralen was injected into rat frontal cortex, where it was metabolized by CYP2B to a reactive metabolite which covalently bound to the active enzyme rendering it inactive and irreversibly radiolabeled (Figure 2). After sacrifice of the animals, radiolabeled CYP2B was retrieved from brain tissue to quantify levels of the functional enzyme. Selectivity of this method was demonstrated by 1) pre-treatment with an injection of a non-radiolabeled CYP2B inhibitor, C8-xanthate, into one side of the brain (Figure 2c), which significantly reduced the yield of ^{3}H-8-methoxypsoralen-radiolabelled CYP2B relative to the non-pretreated side and 2) immunoprecipitation of the radiolabeled protein using an anti-CYP2B antibody. This methodology provides an approach to determine brain enzyme activity *in situ* in a living animal in the presence of enzymes from other organs such as the liver.

Induction of brain CYPs

The expression of a specific CYP within an organ can increase substantially in response to certain chemical agents known as inducers. Many known hepatic CYP inducers have similar effects in the brain, such as the induction of CYP2B by phenobarbital [12]; CYP1A1 induction by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [13]; and CYP2E1 induction by ethanol and acetone [14]. Induction can also be organ specific indicating the differential regulation of hepatic and brain CYPs. For instance, CYP2D is essentially non-inducible in the liver, but brain CYP2D can be induced by compounds such as nicotine (Figure 1e) and the neuroleptic drug clozapine [15, 16].

The regulation of CYPs in the brain is complex, with brain region- and cell-specificity for a particular inducer. For example, in monkeys, chronic nicotine treatment induced CYP2D6

levels in the putamen, substantia nigra, brainstem, cortex, hippocampus and cerebellum, whereas other brain regions, such as the nucleus accumbens and globus pallidus, were unaffected [16]. The cell-specificity of CYP2D6 induction by nicotine is apparent in the cerebellum, where CYP2D6 was increased in Purkinje cells, but not in cells in the molecular or granular layer (Figure 1d and 1e) consistent with the higher levels of staining in human Purkinje cells of smokers compared to nonsmokers (Figure 1b and 1c).

Brain CYPs are regulated by transcriptional, post-transcriptional and post-translational mechanisms. For example, in rat brain, the induction of CYP2E1 by ethanol can occur via a transcriptional mechanism and by protein stabilization [17, 18], whereas the induction of CYP2E1 by nicotine is not accompanied by an increase in mRNA or protein stabilization and may involve an increase in translational efficiency [19, 20]. Generally, the molecular mechanisms underlying the regulation of brain CYP expression are poorly understood.

Insight into the functional role of CYPs in the brain

In humans, individual differences in CYP-metabolism in the brain, for example due to induction, inhibition or genetic variation, may contribute to observed differences in the sensitivity to psychoactive drugs and neurotoxins and may also impact endogenous signaling systems.

The influence of CYP2D6 on brain activity and personality

In vitro studies suggest that CYP2D6 may be involved in the biosynthesis of important endogenous signaling molecules in the brain, such as dopamine and 5-hydroxytryptamine [21, 22]. The gene encoding *CYP2D6* is highly polymorphic, resulting in a wide range of CYP2D6 activity among individuals. Approximately 7% of Caucasians have gene variants that lead to a complete lack of functional enzyme and are referred to as *CYP2D6* poor metabolizers [23]. Both hepatic and brain levels of CYP2D6 are reduced in genetic *CYP2D6* poor metabolizers [5]. *CYP2D6* poor metabolizers may have observable differences in brain function and behavior which may be due to altered production of endogenous signaling molecules. Increased anxiety and impulsivity have been associated with being a *CYP2D6* poor metabolizer [24], giving some indirect support to this concept. Compared to *CYP2D6* extensive metabolizers, poor metabolizers have increased cerebral activity in the thalamus and hippocampus, two regions that have high expression of CYP2D6 protein and mRNA [25]. Genetic variation in *CYP2C19*, which metabolizes testosterone and progesterone, has also been associated with specific personality traits such as reward dependence, cooperativeness and self-transcendence [26, 27].

CYP2B influences sensitivity to centrally acting drugs and affects drug response and behavior

The response to centrally acting drugs is variable and is not always predicted by plasma levels of the drug [28]. Inter-individual differences in brain CYP-mediated metabolism may contribute to this observed variability. Establishing a role for brain CYPs in modulating the effects of drugs has been difficult due to the challenge of distinguishing the effects of hepatic metabolite production from that of the brain. However, it was recently shown that brain CYPs can have a meaningful impact on local drug metabolism and the resulting drug effect in the brain [29] (Figure 3). Rats were given intracerebroventricular (ICV) injections of a CYP2B inhibitor which selectively inhibited the enzyme in the brain, leaving hepatic metabolism unaffected. Upon administration of the anesthetic propofol, which is metabolically inactivated by CYP2B, inhibitor-treated animals had significantly greater sleep times (~2-fold) compared to vehicle-treated animals. Rats were also treated chronically with nicotine, which induces CYP2B in the brain but not the liver [7]; induction of CYP2B

by nicotine treatment reduced propofol-induced sleep time. Inhibition and induction of brain CYP2B increased and decreased brain propofol levels respectively, while not affecting plasma levels, and brain propofol levels were correlated with sleep times. Thus, CYP2B contributes meaningfully to the metabolism of propofol within the brain and to the resulting drug response, demonstrating that brain CYPs can influence response to centrally acting drugs. Brain CYPs can metabolize many drugs that act on the CNS, and therefore there is the potential for brain CYPs to impact the response to a wide array of drugs and toxins.

Many centrally acting drugs are limited by poor uptake into the brain. Increased drug delivery to the brain can be achieved by creating a prodrug that easily penetrates the blood brain barrier, which is then metabolized to the active compound by enzymes present in the brain. Cyclophosphamide is an example of a chemotherapeutic prodrug that is used to treat CNS tumours; the drug passes easily through the blood-brain barrier, where it is metabolically activated by brain CYP2B. Stem cell and gene-directed therapies that increase CYP2B expression selectively in brain tumours can increase the chemotherapeutic effect of cyclophosphamide in mice [30, 31]. The metabolic activation of prodrugs by enzymes within the brain may be a new therapeutic approach to reduce systemic side effects.

Brain CYP3A4 induction is positively associated with altered steroid metabolism as well as cognitive and behavioral dysfunction

Anti-epileptic drug s such as oxcarbazepine, carbamazepine and phenytoin are potent inducers of CYP3A4 in human hippocampal pyramidal neurons [32]. CYP3A4 metabolizes testosterone and estradiol [33, 34], both of which are neuroactive steroids that can influence mood, behavior, sexuality, memory and cognition [35]. The hippocampus is a predominant site for the synthesis and action of testosterone and estradiol [36, 37]. Therefore, induction of CYP3A4-mediated metabolism in this brain structure may have important consequences. The incidence of mood and cognitive changes is increased in epilepsy patients compared to healthy control populations [38, 39]; these changes are more pronounced in epilepsy patients treated with anti-epileptics, suggesting anti-epileptic therapy may modulate steroid levels [40]. Anti-epileptic-treated patients have higher expression of both androgen receptor and CYP3A4 in the hippocampus compared to untreated epileptic patients [32]. Similarly, administration of phenytoin to mice led to the induction of androgen receptor and CYP3A11 (one of the mouse isoform of CYP3A) expression in the hippocampus [41]. The phenytoin-treated mice also had higher levels of CYP19, which metabolically converts testosterone to estrogen [8]. Compared to controls, phenytoin-treated mice had a relatively large reduction in testosterone levels in the hippocampus (38%), whereas plasma levels of testosterone were slightly increased (10%). Testosterone metabolism was increased in hippocampal tissue from phenytoin-treated mice compared to untreated-mice. Inhibition studies, using CYP3A-specific antibodies, confirmed that the observed increase in testosterone metabolism was predominantly CYP3A-dependent, although CYP19 may also contribute. Thus, it is possible that the induction of CYP3A in the hippocampus by anti-epileptics could be increasing local testosterone metabolism, depleting levels of testosterone in the hippocampus and causing a compensatory increase in the androgen receptor.

The endocrine dysfunction associated with the induction of CYP3A4 illustrates how brain CYPs can potentially modulate the local concentrations of endogenous molecules and affect brain function and behaviour. Another example is the CYP1A1- and CYP1A2-mediated metabolism of arachadonic acid in the brain, which produces epoxyeicosatrienoic acid (ETTs) and hydroxyeicosatetraenoic acids (HETEs) known to participate in critical biological processes, such as calcium signaling, vesicle release and the vasodilation of cerebral arteries (se ref [1, 42] for review).

Brain CYPs and drug dependence

Smokers and alcoholics have higher levels of CYP2B6, CYP2E1 and CYP2D6 in specific brain regions and cell types [3–5]. This may represent an important adaptation that contributes to the development or maintenance of nicotine and/or alcohol dependence. Also, smokers and alcoholics may respond differently to certain drugs and toxins due to elevated levels of CYPs in the brain.

Nicotine is the primary psychoactive component of cigarette smoke [43]. In humans and non-human primates the majority of nicotine is metabolized in the liver by CYP2A6 [44]. However, in the brain, CYP2A6 is not expressed to any great extent, whereas CYP2B6, which can also metabolize nicotine, is expressed. In rats, where hepatic and CNS-mediated nicotine metabolism is mainly by CYP2B, the most abundant brain nicotine metabolites are cotinine and nornicotine. Nornicotine has reinforcing properties and can reduce nicotine self-administration in rats [45, 46]. This metabolite may help relieve nicotine withdrawal and may be useful as a pharmacotherapy for smoking cessation. The *CYP2B6* gene is polymorphic; smokers who are genetically *CYP2B6* slow metabolizers had increased withdrawal, higher craving and lower quit rates [47, 48]. *CYP2B6* slow metabolizers do not have altered peripheral metabolism of nicotine [49], therefore the observed impact on smoking behaviors may be due to differing nicotine metabolism within the brain. Decreased CYP2B6-mediated metabolism, leading to increased nicotine and decreased nornicotine in the brains of slow metabolizers, may increase the rewarding effect of smoking and increase withdrawal symptoms during abstinence.

Brain CYPs and neurodegenerative disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterized by the loss of dopamine-producing pigmented neurons in the substantia nigra. Genetic variation, as well as exposure to environmental toxins such as pesticides, is known to influence the risk for developing PD. *CYP2D6* poor metabolizers are at a higher risk for developing PD [50], and this risk is further increased when these individuals are exposed to pesticides [51]. This suggests that faster CYP2D6 metabolism may have a protective effect against PD and in particular reduce PD risk associated with pesticide exposure while lower levels of brain CYP2D6 might put people at risk for not being able to inactivate these toxins. This hypothesis is supported by a recent study showing that individuals with PD had ~40% lower levels of CYP2D6 protein in several brain regions compared to healthy case-matched control individuals, even when controlling for genetic variation in *CYP2D6* [52].

CYP2D6 metabolically inactivates several neurotoxins, including PD-inducing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its toxic metabolite 1-methyl-4-phenylpyridinium (MPP^+) [53]. CYP2D6 is expressed within PD-affected brain regions (for example within the pigmented neurons of the substantia nigra [5, 54]) and is thus ideally situated to participate in the local inactivation of PD-causing neurotoxins. In contrast, inhibition of CYP2D6 in human neuroblastoma cells increased the neurotoxic effects of MPP^+ [53].

Compared to non-smokers, smokers are 50% less likely to develop PD and they have higher levels of brain CYP2D6 (with no change in hepatic CYP2D6), including 3.5-fold higher levels in the substantia nigra [5, 55]. Nicotine induces CYP2D6 in monkey brain but not liver and is therefore thought to be the agent responsible for the higher levels in the brains of smokers (Figure 1b–e). Elevated levels of CYP2D6 in the brain, due to genetics and/or induction by nicotine, may decrease susceptibility to neurotoxicity from toxins inactivated by this enzyme.

Some studies have reported an inverse relationship between caffeine intake and risk for Parkinson's disease, suggesting that variation in CYP1A2-mediated caffeine metabolism in the brain may also influence risk for developing Parkinson's diseases [56]. A deficiency in brain CYP19 has also been identified as a potential risk factor for the development of Parkinson's disease [57]. CYP19 catalyzes the formation of 17β-estradiol, a steroid hormone with neuroprotective effects on the dopaminergic system [8]. *CYP19*-knockout mice are more vulnerable to MPTP-induced dopamine depletion in the substantia nigra compared to *CYP19*-expressing control mice [57]. In addition, genetic variation in *CYP19* and *CYP46* have been associated with increased susceptibility to Alzheimer's disease [58, 59], adding further evidence for the potential role for brain CYPs in modulating neurotoxicity/neuroprotection and influencing the development of neurodegenerative disease.

Concluding remarks

In summary, CYPs are present and active in the mammalian brain. They are expressed in a region-and cell- specific manner, and can be induced by a variety of drugs and toxins. CYP-mediated metabolism within the brain can meaningfully impact the pharmacological response to a psychoactive drug [29]. There is also growing evidence to suggest that CYPs in the brain influence personality and behavior, brain activity, susceptibility to neurotoxins, the development/maintenance of drug dependence, and the risk of developing certain CNS diseases.

Understanding the functional significance of brain CYPs may be valuable in developing more effective approaches to treat and prevent CNS diseases. However, the application of brain CYP metabolism to improve health care and drug development requires advancement in key areas. First, the molecular mechanisms regulating the region- and cell-specific expression of CYPs in the brain, and the impact of inducers and inhibitors, must be better understood. Second, the impact of various brain CYP isoforms on drug/toxin sensitivity and response needs further investigation. This task is made easier by the recent development of animal models that can test the effect of selective brain CYP inhibition or induction on drug response. These include the pharmacological inhibition of brain CYPs via intracerebral injections of a mechanism based inhibitor [29] and the generation of transgenic mice with specific knockouts for CYP or CYP reductase activity in brain, brain regions or brain cell types (e.g. neuron-specific) [60]. Lastly, human studies that incorporate genotyping for relevant CYP genetic variants and brain imaging techniques can offer valuable information about the role of brain CYPs. Also, with the increased use of electronic medical records, patient information will become more accessible, facilitating studies that associate the incidence and severity of certain CNS diseases with CYP genotype and exposure to CNS CYP inducers and inhibitors.

In conclusion, the importance of CYPs in the brain is becoming increasingly clear. The understanding of the roles and regulation of brain CYPs is progressing quickly and may be useful for the development of novel strategies to better predict, prevent and treat disease.

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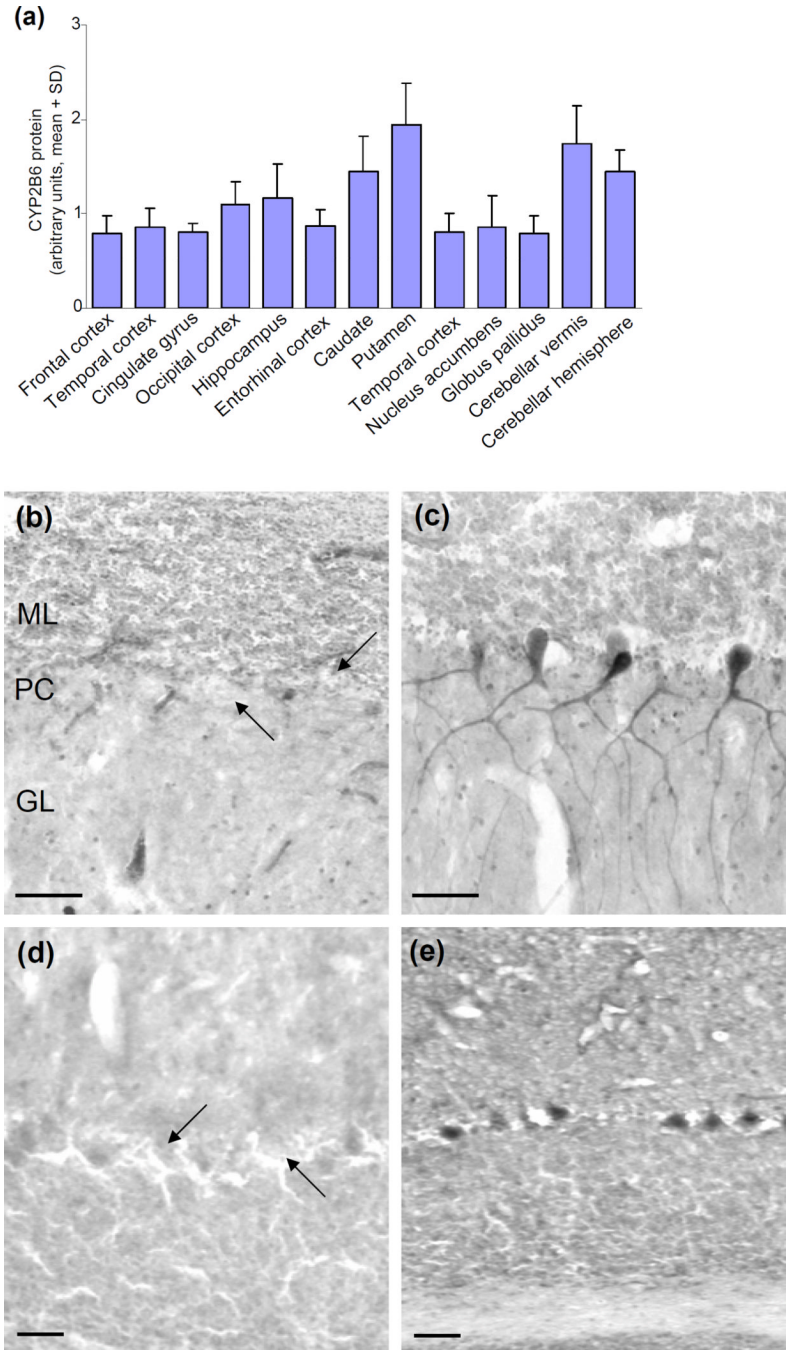

Figure 1. Brain CYP expression is cell-specific, region-specific and inducible

(a) Variation in CYP2B6 protein levels among region in the human brain (ANOVA p=0.026, n= 14). The expression of CYP2D6 in cerebellar Purkinje cells is higher in smokers (c) compared to a non-smokers (b). CYP2D6 is induced in the Purkinje cells within the cerebellum of monkeys chronically treated with nicotine (e) compared to saline-treated monkeys (d). Molecular layer (ML), Purkinje cells (PC) and granular layer (GL) are indicated. Arrows indicate individual Purkinje cells. Bar: 100 μM. Data has been reformatted from Miksys *et al.* 2003 and Mann *et al.* 2008 [3, 16]

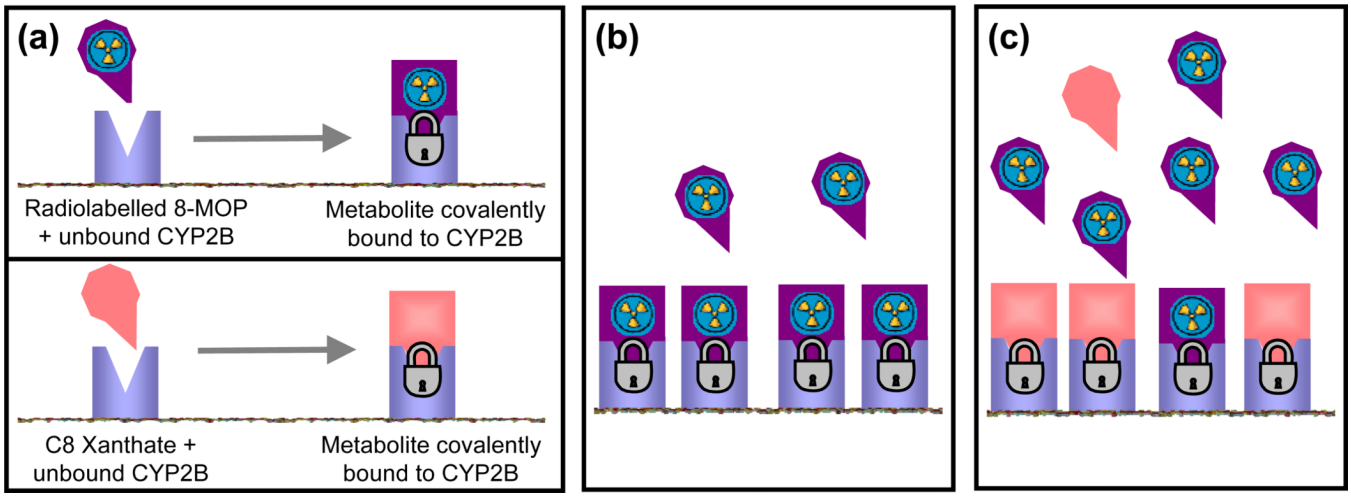

Figure 2. Demonstration of *in situ* metabolism by brain CYP2B in a live animal

(a) The mechanism based inhibitors ^{3}H-8-methoxypsoralen (8-MOP) and C8-xanthate are metabolized by CYP2B to reactive metabolites that covalently bind to the enzyme rendering it inactive. (b) Upon injection of radiolabeled 8-MOP into rat brain, it is metabolized by CYP2B and the enzyme is irreversibly radiolabeled by the metabolite. Following sacrifice, radiolabeled CYP2B can then be retrieved from brain tissue to quantify enzymatic activity which had occurred *in vivo*. (c) Pretreatment with an injection of non-radiolabeled C8-xanthate, into one side of the brain, significantly reduces the yield of radiolabeled CYP2B relative to the non-preinhibited side.

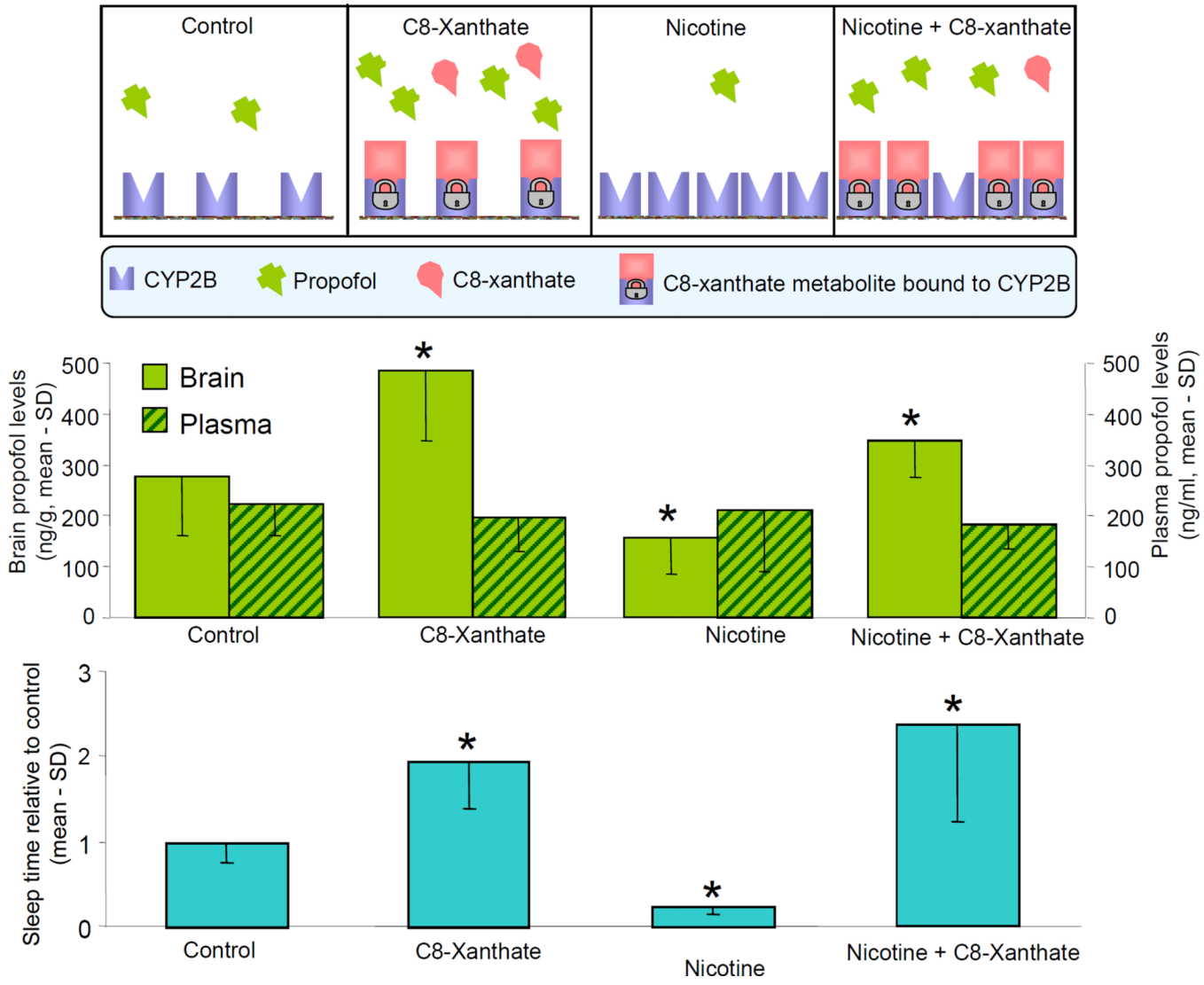

Figure 3. Inhibition and induction of brain CYP2B alters brain propofol levels and response to the anesthetic propofol

Rats were given intracerebroventricular injections of C8-xanthate (a CYP2B inhibitor) and/or chronic nicotine treatment (brain, but not hepatic, CYP2B inducer), which selectively inhibit or induce CYP2B metabolism in the brain, leaving liver CYP2B metabolism unaffected. Following propofol treatment (80 mg/kg i.p.), brain concentrations of propofol were higher in the C8-xanthate-treated rats and reduced in the nicotine-treated rats, compared to baseline. Plasma concentrations of propofol were unaffected by C8-xanthate and/or nicotine treatment. Consistent with changes in brain propofol levels, propofol induced sleep time was longer in the C8-xanthate-treated rats and shorter in the nicotine-treated rats, compared to sleep time at baseline. C8-xanthate treatment (CYP2B inhibition) reversed the nicotine-mediated reductions in brain propofol levels and sleep time. The full study is described in a publication by Khokhar and Tyndale, 2011 [29].

Table I

Examples of CYPs (families 1–4) expressed in the brain grouped according to their centrally acting substrates

Exogenous substrates					Endogenous Substrates		
Clinical drugs			Neurotoxins	Drugs of abuse	Fatty acids	Steroids	Neurotransmitters
Antidepressants	*Antipsychotics*	*Other*	CYP1A	CYP2B	CYP2J	CYP1A	CYP2B
CYP1A	CYP1A	CYP1A	CYP1B	CYP2D	CYP2U	CYP1B	CYP2D
CYP2B	CYP2D	CYP2B	CYP2D	CYP2E1	CYP4A	CYP2B	
CYP2C	CYP3A	CYP2C	CYP2E1			CYP2C	
CYP2D		CYP2D	CYP3A			CYP2D	
CYP3A		CYP2E1					
		CYP3A					