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**Fig. S1:** Basal and induced brain cytochrome P450 enzymes (CYPs) are enzymatically active. CYP2B enzyme activity is assessed by injection of radiolabelled 8-methoxypsoralen into the frontal cortex of a living rat, followed by immunoprecipitation of radiolabelled CYP2B. Panel 1 shows that CYP2B activity is reduced in the right (filled diamond) compared with left frontal cortex (open diamond) by pretreatment with the CYP2B-specific inhibitor C-8-xanthate (C8X). Panel 2 shows that frontal cortex CYP2B activity is increased in nicotine-treated (open square, 1 mg/kg subcutaneously for 7 d) compared with saline-treated (open diamond) rats, and that pretreatment with inhibitor (C8X, filled square) reduces the activity of nicotine-induced CYP2B, indicating that induced brain CYPs are functional. Results were reported as means and standard errors, *n* = 4, "p < 0.05 relative to no inhibitor (panel 1) or saline (panel 2), Student *t* test. Adapted from Miksys and Tyndale.103

**Fig. S2:** Changes in brain CYP2B activity alter propofol-induced sleep times. Propofol is inactivated by CYP2B. Panel 1 shows that inhibition of brain CYP2B activity by intracerebroventricular (ICV) injection of the CYP2B inhibitor C-8-xanthate (C8X) increases sleep time compared with ICV injection of artificial cerebrospinal fluid (ACSF; control), and induction of CYP2B activity by nicotine treatment (1 mg/kg subcutaneously for 7 d) reduces sleep time compared with subcutaneous injection of saline (control). Panel 2 shows that brain levels of propofol are higher after inhibition and lower after induction of brain CYP2B activity. Panels 3 and 4 show that ICV injection of CYP2B inhibitor (C8X) has no effect on plasma propofol levels or on liver CYP2B activity assessed ex vivo. Results were reported as means and standard errors, *n* = 8–16, "p < 0.05 relative to ICV injection of ACSF or subcutaneous injection of saline, Student *t* test. Adapted from Khokhar and colleagues.107

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Fig. S3: Changes in brain CYP2B activity alter chlorpyrifos-induced neurotoxicity. Chlorpyrifos is activated by CYP2B to the neurotoxic oxon; data are shown at 4 hours after treating rats with chlorpyrifos. Inhibition of brain CYP2B activity by 24 hours pretreatment with intracerebroventricular injection of C-8-xanthate (C8X) reduces the righting reflex score, which is an improvement in this behavioural measure of neurotoxicity. Panels 1 and 2 show that inhibition of brain CYP2B activity decreases brain oxon levels and decreases acetylcholine esterase (AChE) inhibition, which is an improvement in this biochemical measure of chlorpyrifos toxicity. Panels 4 and 5 show that plasma chlorpyrifos (CP) and AchE inhibition are unaltered by brain CYP2B inhibition. Results were reported as means and standard errors, n = 4–6, *p < 0.05, least significant difference test. Adapted from Khokhar and Tyndale.

Fig. S4: Inhibition of brain CYP2B activity increases nicotine withdrawal. Continuous intracerebroventricular infusion of the CYP2B inhibitor C-8-xanthate (C8X; 20 µg/d) compared with artificial cerebrospinal fluid (ACSF) increases and delays the peak of spontaneous nicotine withdrawal (arrows). Two-way analysis of variance, drug p = 0.002, time p = 0.001, interaction p = 0.006, n = 8. Total withdrawal (area under the curve), peak withdrawal and time of peak withdrawal are significantly greater for rats that received C8X compared with those that received ACSF (Student t test, all p < 0.05).
Fig. S5: Nicotine induction of CYP2D is organ-specific. CYP2D assessed by immunoblotting is similar in the livers but higher in the brains of rats and monkeys treated with nicotine (1.0 mg/kg subcutaneously daily for 7 days and 0.3 mg/kg subcutaneously twice daily for 21 days, respectively) compared with saline-treated controls. It is also similar in the livers but higher in the brains of human smokers compared with nonsmokers. Results were reported as means and standard errors, \( n = 4–6 \), \( * p < 0.05 \) compared with control or nonsmoker, Student t test.

Fig. S6: Induction of CYP2E1 in rat brain regions is inducer-specific. The pattern of induction of CYP2E1 across rat brain regions assessed by immunoblotting is different for nicotine (1 mg/kg subcutaneously for 7 days) compared with ethanol (3 g/kg orally for 7 days). Results were reported as means and standard errors, \( n = 4 \), \( p < 0.05 \), Student t test. Adapted from Howard and colleagues.

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**Fig. S7:** Nicotine induction of CYP2B across brain regions is species-specific. The pattern of induction of CYP2B across brain regions assessed by immunoblotting is different in nicotine-treated rats (1 mg/kg subcutaneously for 7 days, n = 4) compared with monkeys (0.3 mg/kg subcutaneously twice daily for 21 days, n = 6). Results were reported as means and standard errors, *p < 0.05 compared with saline-treated controls, Student t test. Adapted from Mikys and colleagues51 and Lee and colleagues.142

**Fig. S8:** Nicotine induction of cytochrome P450 enzymes (CYPs) across rat brain regions is isozyme-specific. In rats treated with nicotine (1.0 mg/kg subcutaneously for 7 days) the pattern of induction across brain regions is different for CYP2B, CYP2D and CYP2E1, as assessed by immunoblotting. Results were reported as means and standard errors, n = 4, *p < 0.05 compared with saline-treated controls, Student t test. Adapted from Howard and colleagues45 Mikys and colleagues51 and Yue and colleagues.121