A HERBICIDE PYRIBUTICARB IS MORE POTENT INDUCER OF CYP3A4 EXPRESSION INTERACTING WITH PREGNANE X RECEPTOR THAN RIFAMPICIN
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Pesticides are used all over the world. However influence of them on our bodies is not well known. Using a CYP3A4 reporter system, we show that pesticides activate the CYP3A4 promoter interacting with human pregnane X receptor (hPXR). Among the pesticides examined, pyributicarb, isoxathion, ditiopyr, dymron and isophenfos strongly activated the CYP3A4 reporter (bases -362 to +11 and -7836 to -7008) in HepG2-derived cells stably expressing the CYP3A4 reporter gene. Especially, pyributicarb potently activated the CYP3A4 reporter at lower concentrations (0.1 – 3 µM) than rifampicin and clotrimazole did. Introduction of hPXR-siRNA dramatically inhibited the pyributicarb-stimulated activation of the CYP3A4 reporter and also inhibited the increase of endogenous CYP3A4 mRNA levels in HepG2 cells. In addition, pyributicarb activated CYP3A4 reporter depending on introduction of hPXR in CV-1 cells. These results indicate that pyributicarb more potently induce CYP3A4 expression interacting with hPXR than rifampicin. Currently we are investigating whether these pesticides induce Cyp3a expression in mouse liver. Our results presented that the pesticides, as well as the drugs, should be developed in consideration of human P450 induction and inhibition.

INDUCTION OF CYP3A BY DEXAMETHASONE IN RAT SMALL INTESTINE AND LIVER
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CYP3A is the most abundant CYP subfamily in the liver and small intestine, and the bioavailability of orally administered CYP3A substrates is influenced by the first-pass metabolism in both organs. Since there is no method to predict the small intestinal first-pass effect in humans, we attempted to use dexamethasone (DEX) treated rats as a model to evaluate the small intestinal first-pass effect. In this study, we investigated the effects of the dose and the treatment time of DEX on the induction of CYP3A in the small intestine and liver of rats. Microsomes were prepared from the small intestine and liver, and the metabolism of testosterone (TST) was measured in the presence of the microsomes. The CYP3A activity was evaluated based on the formation rate of 6-beta-hydroxytestosterone. Microsomes were prepared at 6-24 h following single oral administration of DEX or after 2-4 days of once-daily oral administration of DEX. The CYP3A activity was maximal at 12-24 h in the small intestine, whereas the activity in the liver was maximal after 4 days of administration. The activity was approximately 3- and 11-fold greater than that of the control in the small intestine and liver, respectively.

Various doses of DEX were orally administered and the microsomes were prepared at 24 h following administration. The CYP3A activity in the small intestine was maximal at a dose of 20 mg/kg, and it was approximately 3-fold greater than that of the control. CYP3A activities at higher doses of DEX were similar to that at 20 mg/kg. On the other hand, the CYP3A activity in the liver was maximal at 200 mg/kg, with the activity being approximately 4-fold greater than that of the control.

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