EFFECT OF PSYCHOTROPIC DRUGS ON THE 21-HYDROXYLATION OF NEUROSTEROIDS, PROGESTERONE AND ALLOPREGNANOLONE, CATALYZED BY RAT CYP2D4 AND HUMAN CYP2D6 IN THE BRAIN
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We have reported that rat CYP2D4 and human CYP2D6 catalyze the 21-hydroxylation of neurosteroids, such as progesterone (PROG) and allopregnanolone (ALLO), and that fluoxetine, a selective serotonin reuptake inhibitor, inhibited ALLO 21-hydroxylation by rat brain microsomes. In this study, we investigated the effects of psychotropic drugs, such as fluoxetine, imipramine (tricyclic antidepressant, serotonin and noradrenaline reuptake inhibitor), desipramine (noradrenaline reuptake inhibitor), mazindol (monoamine reuptake inhibitor), and GBR12909 (dopamine uptake inhibitor), on the 21-hydroxylation of PROG and ALLO mediated by CYP2D4 and CYP2D6 in order to clarify the possibility that neurosteroid levels are affected by psychotropic drugs in the brain. PROG and ALLO were incubated with CYP2D4 or CYP2D6 in the presence of NADPH, and the 21-hydroxylated metabolites of PROG and ALLO were analyzed by HPLC and LC/MS/MS, respectively. All drugs investigated competitively inhibited the PROG 21-hydroxylation by CYP2D4 and/or CYP2D6, and the drugs except for mazindol competitively inhibited the ALLO 21-hydroxylation by CYP2D4. The present study suggests that these psychotropic drugs modify the regulation of brain levels of neurosteroids.

DO DATA FROM MINIPIGS HELP PREDICT IN VIVO DDI IN HUMANS?

Minipigs have been used as experimental animals for a long time. The activity and amino acid sequence of hepatic CYP3A is reported to be similar in humans and minipigs. However, little is known about effects of typical inhibitors of human CYP3A on minipig CYP3A. Additionally, there has been no report of an in vivo drug-drug interaction (DDI) study in minipigs. The purpose of this study was to determine whether minipigs could be used to assess the risk of DDI. Thus, CYP3A inhibition, both in vitro and in vivo, was evaluated during this study. The $K_m$ value for midazolam 1'-hydroxylation by minipig liver microsomes was 4.6 μM, and the $K_m$ value for testosterone 6β-hydroxylation was 56 μM. The IC$_{50}$ of midazolam 1'-hydroxylation by antifungal azoles (ketoconazole and itraconazole) and statins (simvastatin and lovastatin) in vitro were determined for human, minipig and rat liver microsomal systems. The IC$_{50}$ values were quite similar in human and minipigs, whereas the value for rats was quite different. Furthermore, results of an in vivo DDI study show that the AUC of midazolam after oral administration (0.5 mg/kg) to male minipigs (NIBS, institution Nihon Bio Research Inc.) increased 7.1-fold when it was coadministered with ketoconazole (6.6 mg/kg, oral). This result agrees with predictions made from the in vitro IC$_{50}$ value using a physiological model, and is similar to the well-known DDI observed in human. These data indicate that the minipig is a potentially useful animal to validate predictions of CYP3A-mediated in vivo DDI from in vitro parameters.