Propofol metabolism is enhanced after repetitive ketamine administration in rats: the role of cytochrome P-450 2B induction.

陳瑞明
Chan WH;Chen TL;Chen RM;Sun WZ;Ueng TH

Abstract

BACKGROUND: In a series of ex vivo and in vivo studies we investigated the ability of repetitive ketamine administration to alter the metabolism and anaesthetic effect of propofol and the role of ketamine-mediated P-450 2B induction in rats. METHODS: Male Wistar rats were pretreated with 80 mg kg(-1) ketamine i.p. twice daily for 4 days. Pentoxyresorufin O-dealkylation (PROD), P-450 2B protein and mRNA were determined. Residual propofol concentration was measured after incubating hepatic microsomes with 100 muM propofol. Sleeping times induced by i.p. 80 mg kg(-1) propofol were determined. Orphenadrine, a P-450 2B inhibitor, was added in both ex vivo and in vivo studies. Finally, serial whole blood propofol concentrations were determined after i.v. infusion of 15 mg kg(-1) propofol. RESULTS: Ketamine pretreatment produced 5.4-, 3.4- and 1.7-fold increases in hepatic PROD activity, P-450 2B protein and mRNA, respectively. Residual propofol concentration was 46% lower after incubation with microsomes from ketamine-pretreated rats than in the control group. The addition of orphenadrine to ketamine-pretreated microsomes produced an increase in residual propofol concentration in a concentration-dependent manner. Ketamine pretreatment reduced propofol sleeping time to 12% of the control, which was reversed by orphenadrine. The whole blood propofol concentration in ketamine-pretreated rats was significantly lower than that of control rats at 1, 2, 4 and 8 min after cessation of propofol infusion. CONCLUSIONS: Repetitive ketamine administration enhances propofol metabolism and reduces propofol sleeping time in rats. We suggest that P-450 2B induction may produce ketamine-propofol interaction in anaesthetic practice.