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

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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 μM 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.

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combination of propofol and ketamine is reported to be particularly useful in anaesthesia for office-based cosmetic surgery\(^6\) and paediatric interventional procedures.\(^7\) Aside from anaesthesia, ketamine can be used in the treatment of chronic\(^8\) and cancer pain.\(^9\) In addition, ketamine is also a popular drug of abuse.\(^10\)

The development of ketamine tolerance after repetitive administration has been reported in humans\(^11\) and rats.\(^12\) Such a phenomenon was proposed to result from the induction of drug-metabolizing enzymes by ketamine.\(^12\) Our laboratory previously showed that repetitive administration of ketamine-induced P-450 1A, 2B, 2E and 3A activities and proteins in rats.\(^13\) The accelerated metabolism of ketamine after multiple doses may be a result of P-450 2B induction as P-450 2B plays an important role in the demethylation of ketamine by human liver microsomes.\(^14\) However, the effect of ketamine-mediated P-450 induction on the biotransformation of another drug has not been specifically addressed. The induction of P-450 is recognized as a common mechanism of drug–drug interaction. Therefore, we conducted this study to investigate the effect of repetitive administration of ketamine on the metabolism and anaesthetic effect of propofol in rats, and the role of P-450 2B induction in drug–drug interaction.

**Methods**

**Chemicals and animal treatment**

Propofol was kindly provided by AstraZeneca Corp. (Macclesfield, England, UK). Ketamine hydrochloride and orphenadrine hydrochloride were purchased from Sigma Chemical Corp. (St Louis, MO, USA). Male Wistar rats weighing 180–200 g were pretreated with 80 mg kg\(^{-1}\) ketamine i.p. twice a day for 4 days.\(^13\) Rats were killed by decapitation 24 h after the last dose of ketamine and livers were removed for histological examination, microsomal preparation and RNA isolation. Blood samples were collected and centrifuged at 2500 \(g\) for 10 min. Serum alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase activities were determined using a TBA-200FR Automated Analyser (Toshiba, Tokyo, Japan). The normal ranges for serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in untreated rats are 80–120, 40–60 and 400–600 U litre\(^{-1}\), respectively.\(^13\)

**Hepatic microsomal preparation**

Three grams of liver were homogenized in 1.15% potassium chloride and centrifuged at 9000 \(g\) for 20 min. The supernatant was further centrifuged at 105 000 \(g\) for 1 h. The pellet was resuspended and centrifuged at 105 000 \(g\) for 1 h again, then covered with 0.1 M potassium phosphate buffer solution (pH=7.4) and stored at \(-70^\circ\)C until use. Microsomal protein concentration was determined by the method of Lowry and colleagues\(^15\) using bovine serum albumin as a standard.

**Determination of pentoxyresorufin O-dealkylation (PROD) activity**

Hepatic microsomal PROD activity, a sensitive assay for the activity of P-450 2B, was determined after the fluorometric method of Lubet and colleagues\(^16\) as previously published.\(^13\) The incubation system contained microsomal protein 0.5 mg, NADPH 0.15 mM, MgCl\(_2\) 25 mM, bovine serum albumin 1.8 mg and pentoxyresorufin 10 \(\mu\)M in Tris buffer (0.1 M, pH 7.5) to a final volume of 1 ml. The reaction was started in a 37°C shaking water bath and continued for 10 min in a dark room. The product of the reaction, resorufin (RF), was measured fluorometrically at excitation and emission wavelengths of 522 and 586 nm, respectively. Rho- damine B, from 0.01 to 0.1 \(\mu\)M, was used as a standard and all readings in this study fell within the linear range of the standards. In the in vivo experiment, ketamine-pretreated rats were killed 24 h after the last dose of ketamine, while orphenadrine-treated rats were killed 2 h after the treatment. In the in vitro inhibition study, 0, 10, 30, 50, 80 and 100 \(\mu\)M orphenadrine respectively were incubated with microsomes and NADPH at 37°C for 20 min before pentoxyresorufin was added into the incubation mixture, allowing the generation of reactive metabolite for specific enzyme inhibition.\(^3\)

**Gel electrophoresis and immunoblot analysis**

Twenty micrograms of microsomal protein were subjected to sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) procedure according to Laemmli’s method.\(^17\) The final concentration of acrylamide in the separating gel was 7.5%. After electrophoresis, proteins in the gel slab were transferred electrophoretically onto a nitrocellulose membrane after the method of Towbin and colleagues.\(^18\) The nitrocellulose paper was then incubated with blocking buffer containing 5% non-fat milk for 20 min. A mouse monoclonal antibody (MAb) 2-66-3 raised against phenobarbital-inducible rat P-450 2B1/2, kindly provided by Dr Sang S. Park (Occupational Diseases Diagnosis and Research Center, Industrial Research Institute, Korea Industrial Safety Corporation, Inchon, Korea), was used as the primary antibody as previously published.\(^13\) The primary antibody was incubated with membrane overnight at 4°C. After washing off the primary antibody, the membrane was incubated with the goat anti-rabbit immunoglobulin horseradish peroxidase-linked whole antibody at room temperature for 2 h. An enhanced chemiluminescence system (Amersham Biosciences UK Ltd, Little Chalfont, Buckinghamshire, England, UK) was used to see the immunoreactive protein bands. Intensities of the immunoreactive bands were determined using an IS-1000 Digital Imaging System (Alpha Innotech Corporation, San Leandro, CA, USA).
RNA isolation and semi-quantitative reverse transcriptase–polymerase chain reaction (RT–PCR)

Total hepatic RNA was isolated using the acid guanidinium thiocyanate–phenol–chloroform method of Chomczynski and Sacchi.19 RNA concentrations and purities were checked spectrophotometrically by the ratio of absorbance at the wavelength of 260–280 nm. cDNA was obtained by incubating RNA with reaction buffer containing Moloney Murine Leukaemia Virus Reverse Transcriptase (M-MLV RT) from Invitrogen Corp., Carlsbad, CA, USA according to the manufacturer’s suggestion. Briefly, a 20 μl reaction mixture was prepared containing 1 μl oligo(dT)15, 400 ng total RNA, 1 μl dNTP Mix, 2 μl 0.1 M dithiothreitol, 1 μl RNase-OUT (recombinant ribonuclease inhibitor), 1 μl M-MLV RT and 4 μl reaction buffer containing 250 mM Tris–HCl, 375 mM KCl and 15 mM MgCl₂. The reaction mixture was incubated for 1 h at 37°C followed by inactivation of the enzyme at 95°C for 5 min. The PCR analysis of P-450 2B1/2 and cyclophilin was performed after the procedures by Morris and Davila.20 Cyclophilin is a housekeeping gene that serves as an internal standard in the semi-quantitative PCR analysis. The forward and reverse primers of P-450 2B1/2 were GAGTCTCTCTGGTTCCTG and ACTGTGGGTCA-TGGAGGCGTG. The forward and reverse primers of cyclophilin were CTTGACATACGGCTGATGG and CAGGACCTGTATGCTTCAGG. The PCR products were loaded on 1.5% agarose gels, separated by electrophoresis and was seen using ethidium bromide in ultraviolet light. Expression ratios were calculated by dividing the band intensity of the product by that of the corresponding cyclophilin band.

Microsomal incubation with propofol

Hepatic microsomes (0.5 mg) were incubated with propofol 100 μM and an NADPH-generating system [consisting of 3 mM MgCl₂, 1 mM NADP, 2 mM glucose-6-phosphate (G6P), 5 U ml⁻¹ glucose-6-phosphate dehydrogenase in 0.1 M Tris buffer, pH=7.5] at 37°C for 10 min. G6P concentration at 2 mM was not rate-limiting in the NADPH-generating system because the concentration was near saturation at 69 times of the Km (0.029 mM) of G6P dehydrogenase-catalysed G6P oxidation reaction.21 In addition, 2 mM G6P was as effective as 5 mM G6P in generating NADPH to support propofol metabolism in the 10 min incubation time (data not shown). A previously published paper also reported the use of 5 mM G6P in propofol metabolism study.1 In the enzyme inhibition study, orphenadrine was incubated with microsomal protein from ketamine-pretreated rats and NADPH-generating system at 37°C for 10 min before propofol was added. Then the mixture was incubated in a 37°C shaking water bath for 10 min. Cyclohexane was added into each tube followed by vigorous vortex. The organic layer containing propofol was dried under nitrogen. The extraction product was dissolved using 200 μl mobile phase (60% acetonitrile in distilled water with 0.1% trifluoroacetic acid) for analysis using high-performance liquid chromatography (HPLC). The HPLC system consisted of a Jasco 600S controller, an autosampler 717 plus and a UV detector model 474 (Jasco Inc., Great Dunmow, Essex, UK), with wavelength set at 270 nm.22 The column was Xterra™ RP18 (Waters Corp., Milford, MA, USA). The flow rate was 0.3 ml min⁻¹ and the elution time was 20 min for each sample. The retention time of propofol was approximately 13.8 min. Residual propofol concentration after the incubation was used as an indicator of metabolism.

Determination of propofol sleeping time

Propofol, at the dose of 80 mg kg⁻¹, was administered i.p. 24 h after the last dose of ketamine. Another group of rats were treated with i.p. orphenadrine 100 mg kg⁻¹, a P-450 2B inhibitor, 2 h before propofol administration. The rats were immediately transferred to a dark, quiet room in order to avoid the interference of environmental stimuli. The time to spontaneous righting was recorded in each rat.

Determination of whole blood propofol concentrations

A catheter was inserted into the superior vena cava of each rat and i.v. propofol infusion at the rate of 15 mg kg⁻¹ more than 6 min was started 24 h after the last dose of ketamine. Heparin at the dose of 500 unit kg⁻¹ was given i.v. immediately before propofol infusion. Serial blood sampling was performed at 1, 2, 4, 8, 15, 25, 35, and 50 min after the cessation of the infusion. A total of 100 μl of blood was drawn from the rat and the same volume of saline was administered to the rat at each time point. The determination of whole blood propofol concentration and the preparation of standard solutions were performed after the method published by Knibbe and colleagues.23

Assay validation

In the PROD assay, the average inter- and intra-assay coefficients of variation were 4.70 (1.89)% and 2.56 (2.29)%, respectively. The incubation time linearity was also determined in PROD and ex vivo propofol metabolism studies, showing the correlation coefficients of 0.9279 and 0.9615, respectively. In HPLC analysis of propofol concentration, the detection limit was 0.4 mg litre⁻¹ and the linearity was up to 40 mg litre⁻¹. The average inter- and intra-assay coefficients of variation were 4.92 (3.03)% and 3.68 (4.18)%, respectively. In serum aspartate aminotransferase, the coefficients of variation were 4.92 (3.03)% and 3.68 (4.18)%, respectively.
ANOVA when appropriate. Dunnett test was applied as a post hoc test when significant difference was detected by one-way ANOVA. The level of statistical significance was set at a $P$-value $<0.05$.

**Results**

Body weights, liver weights and liver/body weight ratios were comparable between control and ketamine-pretreated rats. The morphology of livers from ketamine-pretreated rats was grossly normal at the time of death. Histological examination of liver sections using haematoxylin–eosin staining exhibited no pathological changes such as fibrosis or necrosis in ketamine-pretreated rats. The serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in control and ketamine-pretreated rats were 100 (13) and 80 (9), 47 (3) and 46 (4), 484 (38) and 404 (41) U litre$^{-1}$, respectively. Data of liver function test were obtained from three animals in each group and there was no significant difference between the two groups.

The 4-day ketamine treatment produced a 5.4-fold increase in PROD activity of liver microsomes (Fig. 1A). The increased PROD activity in ketamine-pretreated rats was reversed 2 h after the administration of orphenadrine (100 mg kg$^{-1}$). Orphenadrine treatment of rats produced a 52% decrease in the PROD activity in comparison with control rats. The immunoblot analysis of liver microsomal proteins revealed increases in P-450 2B1/2-immunoreactive protein bands in ketamine-pretreated rats (Fig. 1A). P-450 2B1 and 2B2 were closely migrating proteins and their intensities were analysed densitometrically in combination. Ketamine pretreatment produced a 3.4-fold increase in P-450 2B-immunoreactive proteins. The results of RT–PCR analysis of liver RNA revealed that ketamine pre-treatment increased the amount of hepatic P-450 2B mRNA by 1.7-fold (Fig. 1C). Collectively, these data indicated that repetitive ketamine administration induced hepatic P-450 2B catalytic activity, protein and mRNA.

The following study was conducted to investigate the effect of ketamine pretreatment on propofol metabolism ex vivo by incubating propofol with hepatic microsomes in the presence of NADPH. Residual propofol concentration after incubation was used as an index of degree of propofol metabolism. The results demonstrated that residual propofol concentration after incubation with hepatic microsomes from ketamine-pretreated rats was 46% lower than the concentration after incubation with control rat hepatic microsomes [71.5 (5.0) μM in controls vs 38.7 (3.6) μM in ketamine-pretreated rats] (Fig. 2A). In order to investigate the role of P-450 2B induction in this decrease in residual propofol concentration, the P-450 2B inhibitor orphenadrine was added into the propofol and microsome incubation system. The results revealed that orphenadrine produced a concentration-related increase in residual propofol concentration after incubation. The additions of 10, 30, 50 and 80 μM orphenadrine produced 1.1-, 1.3-, 1.5- and 1.9-fold increases in residual propofol in comparison with the incubation without orphenadrine, respectively (Fig. 2A). Correspondingly, orphenadrine produced a concentration-related decrease in PROD in ketamine-pretreated microsomes. The additions of 10, 30, 50, 80 and 100 μM orphenadrine led to 21, 37, 49, 74 and 76% decreases in PROD activity in ketamine-pretreated microsomes, respectively (Fig. 2A). Taken together, the data suggested that orphenadrine inhibited P-450 2B-dependent catalytic activity and reversed the enhanced propofol metabolism in ketamine-induced microsomes ex vivo.

Repetitive ketamine administration produced an 88% reduction in propofol-induced sleeping in comparison with control rats [92 (7) vs 11 (1) min in control and

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**Fig 1** The induction of hepatic P-450 2B by ketamine in rats. (A) P-450 2B-dependent PROD activity (pmol resorufin min$^{-1}$ mg protein$^{-1}$). The increase in PROD activity after ketamine pretreatment was reversed by the addition of orphenadrine, a P-450 2B inhibitor. *Value was significantly different from the control by ANOVA followed by Dunnett test, $P<0.05$. Ctrl: control; Ket: ketamine; Orph: orphenadrine. Each bar represents mean and se. (B) Immunoblot of P-450 2B1/2 proteins. (C) Semi-quantitative RT–PCR analysis P-450 2B1/2 and cyclophilin mRNA. Each group consisted of three animals in PROD and immunoblot experiments and four animals in the RT–PCR analysis experiment.
The administration of ketamine pretreatment did not produce any significant change in propofol sleeping time compared with control rats. However, orphenadrine effectively reversed the reduced sleeping time in ketamine-pretreated rats (120 (12) min in rats pretreated with ketamine and orphenadrine).

To confirm that propofol metabolism was enhanced after ketamine pretreatment in vivo, the following study was carried out to compare the change in whole blood propofol concentrations in ketamine-pretreated and control rats after an i.v. infusion of 15 mg kg⁻¹ propofol. Whole blood propofol concentrations were significantly lower in ketamine-pretreated rats compared with control rats at 1, 2, 4 or 8 min after cessation of propofol infusion (Fig. 4). The propofol concentrations from 15 to 50 min after the cessation of infusion were lower in ketamine-pretreated rats but were not statistically significant. These data showed a faster decline in blood propofol concentration in ketamine-pretreated rats in the first 10 min after cessation of infusion. In this study, the sleeping time after i.v. propofol infusion was recorded in each rat. Ketamine-pretreated rats had significantly shorter sleeping times than those of the controls in this experiment [24 (2) min in controls vs 8 (2) min in ketamine-pretreated rats, P<0.05]. These data further confirmed that the anaesthetic effect of propofol was reduced after repetitive ketamine pretreatment. To determine whether ketamine pretreatment could lead to altered sensitivity to propofol, whole blood propofol concentration at the time of awakening was estimated by interpolation using the time–concentration curve in each rat. There was no significant difference in the whole blood propofol concentration at the time of awakening between the control and the ketamine-pretreated rats [1.98 (0.71) mg litre⁻¹ in controls vs 2.36 (0.55) mg litre⁻¹ in ketamine-pretreated rats, P>0.05].

**Discussion**

This is the first study to demonstrate that repetitive ketamine administration induces P-450 2B1/2 at the level of catalytic activity, protein and mRNA. Hepatic microsomes from ketamine-pretreated rats have an enhanced ability for propofol metabolism and the enhanced propofol metabolism is reversed by the addition of P-450 2B inhibitor orphenadrine in a concentration-dependent manner. Significant reduction of propofol-induced sleeping time is also observed in ketamine-pretreated rats and the reduction is effectively reversed by orphenadrine. Our data clearly demonstrate that P-450 2B induction plays a crucial role in the enhanced metabolism of propofol.
role in ketamine–propofol interaction. The result of this animal study is in agreement with the current view that P-450 2B is an important enzyme responsible for propofol metabolism in humans. The involvement of other P-450 isoforms cannot be ruled out as the P-450 isoforms responsible for propofol hydroxylation in rats have not been fully explored. For example, P-450 1A and 2C subfamilies participate in propofol hydroxylation. Their importance in propofol metabolism in rats has not been clearly defined. Nonetheless, the present data suggest that P-450 2B may occupy a key position in rats as in humans.

The accelerated disappearance of propofol from the systemic circulation is more obvious at relatively higher concentrations in the in vivo study. Therefore, we selected propofol (100 μM) in the ex vivo study. Although only a plasma concentration of 3–4 mg litre⁻¹ (approximately 17–22 μM) is required for the maintenance of anaesthesia during surgery, a plasma concentration of 10 mg litre⁻¹ (~56 μM) can be reached when a single bolus of propofol is given i.v. at the induction of anaesthesia. The concentration of propofol in the liver is reported to be three to four times higher than that in whole blood in rats during the first 15 min after administration of an i.v. bolus dose, and the peak propofol concentration in the liver after a single bolus can be as high as 23 μg g⁻¹ tissue (~130 μM). Accordingly, the concentration of 100 μM propofol used in the ex vivo study is clinically relevant. The results of the ex vivo incubation study are compatible with the initial decrease in whole blood propofol concentration in ketamine-pretreated rats, whereas the difference becomes less prominent at lower propofol concentrations.

In the sleeping time study, propofol was administered i.p. to rats because this route of administration allows good distribution of a potentially irritating drug in a well-perfused space with a large surface area. I.P. administration also generates useful data for anaesthetic effect and modulation of drug-metabolizing enzymes. In addition, the results of the i.v. infusion studies showed reduced propofol sleeping time in ketamine pretreated rats. Therefore, i.p. and i.v. administration generated confirmatory data in this study.

Despite the reduction of propofol sleeping time in ketamine-pretreated rats, it is noteworthy that the duration of propofol action is not solely determined by the activity of a drug-metabolizing enzyme. Other determinants of the anaesthetic effect of propofol, such as pharmacodynamic interactions, cardiac output and hepatic blood flow are not fully elucidated in the study. Even though we did not measure the ketamine concentration in rats at the time of propofol injection, the effect of residual ketamine could be precluded because this drug should have produced an additive effect and prolonged rather than shortened sleeping times. In addition, our data do not support the premise that the reduction in propofol sleeping time is a result of diminished sensitivity to propofol after ketamine pretreatment. Estimated whole blood propofol concentrations on awakening did not differ significantly between ketamine-pretreated and control rats. Brain propofol concentration correlated with blood concentration within 30 min after an i.v. bolus in rats. Therefore, pharmacodynamic regulation seemed less likely to participate in ketamine–propofol interaction. An increased cardiac output or hepatic flow might also contribute to a more rapid decrease in plasma propofol concentration and possibly reduce the propofol sleeping time. Acute treatment with ketamine is known to increase cardiac output and hepatic blood flow but the effect is often short-lived. Evidence of persistent increase in cardiac output and hepatic blood flow after repetitive ketamine pretreatment is lacking. In this study, propofol was given to rats at least 24 h after the last dose of ketamine. Hence the acute effect of ketamine is assumed to be negligible at the time of propofol treatment. Collectively, the potential confounding factors of cardiac output and pharmacodynamic interaction may have minimal effects on ketamine–propofol interaction observed in this study.

It is arguable that metabolic enzymes other than P-450 induction may have contributed to this ketamine–propofol interaction. For instance, propofol can undergo direct conjugation by UDP-glucuronosyltransferase (UGT) other than hydroxylation by P-450. The present data cannot completely rule out the involvement of UGT in the drug–drug interaction because some P-450 2B inducers, such as phenobarbital, are also capable of inducing UGT. However, the propofol–UGT activity measured in liver microsomes is much lower in rats than in humans. A P-450 2B inhibitor almost completely reverses the effect of ketamine pretreatment on propofol sleeping time. Therefore, we suggest that P-450 2B induction plays a major role in the enhanced biotransformation of propofol by ketamine in rats. Our study does not support the contribution of UGT to ketamine–propofol interaction in rats.

To the best of our knowledge this report is the first to demonstrate metabolic interaction between ketamine and

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**Fig 4** The effect of ketamine pretreatment on whole blood propofol concentration in rats (log mg litre⁻¹). Filled circle: control group; open circle: ketamine-pretreated group. Each point represents mean and SE. *Value was significantly different from respective control groups, P<0.05. Each group comprised three animals.
Repetitive ketamine enhances propofol metabolism

Propofol in experimental animals. There are no related case reports of such a drug–drug interaction. Clinical reports of drug–drug interactions concerning some other P-450 2B inducers, such as midazolam,34 are also lacking. Inhibition of drug-metabolizing enzymes by systemic inflammatory reaction was shown to diminish hepatic metabolism of propofol in rabbits,35 implicating that altered P-450 activity could significantly affect propofol metabolism in animals. Whether the ketamine–propofol interaction demonstrated in this study exists in humans, and its clinical significance, need further consideration because the extrapolation from laboratory animals to humans in xenobiotic biotransformation has limitations. Direct conjugation is suggested to be the dominant metabolic pathway (more than 70% of total urinary propofol metabolites) of propofol metabolism in humans.1 In contrast, conjugation to propofol primarily occurs after hydroxylation of an isopropyl group in rats.26 The impact of P-450 induction on propofol metabolism can be less prominent in humans. However, the P-450-dependent propofol hydroxylation can occupy a substantial role in some human subjects and is responsible for up to 60% of propofol metabolism.2 Therefore, the influence of enhanced propofol hydroxylation can be clinically significant in humans.

An additional concern is that the inducibility of P-450 2B can vary among species. Even though enzyme induction by ketamine appeared to develop more slowly and the incidence could be lower in humans compared with rats,11 the effect of P-450 2B induction in humans is substantial as there are a few clinical reports describing multiple doses of P-450 2B inducers, including ketamine, changing the pharmacological properties of subsequently administered drugs.11 36 Consequently, it is possible that long-term ketamine use can alter the metabolism and anaesthetic effect of propofol by P-450 2B induction in humans. The lack of related clinical reports may be explained by the following reasons. Firstly, enzyme induction by xenobiotics needs treatment over a period of time to become clinically significant. Ketamine is more often used as single bolus than as chronic medication. Secondly, clinicians are usually careful in the development of cardiovascular or respiratory complications related to an additive effect when combining these anaesthetics. Inadequate anaesthesia resulting from enhanced drug metabolism may be managed by adding up doses or supplementing adjuvant agents. Finally, the amount of hepatic P-450 2B is highly variable among human subjects (up to 100-fold difference).37 Catalytic activity of propofol hydroxylase in humans had a 19-fold variation, which was mainly attributed to different P-450 2B activities.4 Therefore, the induction of P-450 2B and the resultant effect on propofol metabolism in humans can also show considerable individual differences, unlike the relatively uniform response in rats. As this is the first report of the possible increase in propofol metabolism by repetitive ketamine administration, the actual influence on clinical outcomes needs to be evaluated. The effect of other P-450 inducers on propofol metabolism also needs to be determined.

In conclusion, repetitive ketamine administration enhances the metabolism of propofol and decreases anaesthetic sleeping time in rats. These alterations are mainly attributed to the induction of P-450 2B after ketamine pretreatment. The results indicate the potential for propofol–ketamine interaction in clinical situations. Our study suggests that once ketamine tolerance develops after repetitive treatment, subsequent administration of propofol at the conventionally recommended dose may lead to unpredictably short duration of action or unsatisfactory anaesthetic effect.

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