control 0.50 ± 0.02, ethanol pretreated 0.57 ± 0.06 nmol min^{-1} mg $protein^{-1}$ ($n=7$, $P>0.05$).

One possible explanation for the decrease in the rate of hexobarbitone removal might lie in the release of adrenal cortical hormones by the ethanol. Serum cortisol levels were 4.2 ± 0.5 μg/100 ml ($n=5$) in control animals and 14.5 ± 2.4 μg/100 ml ($n=6$, $P<0.01$) in animals pretreated with ethanol 24 h previously. Corticosterone administered to rats *in vivo* is known to inhibit the hepatic microsomal metabolism of hexobarbitone (Chung & Brown, 1976).

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Influence of age and sex on the duration of action of ketamine in the rat

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In order to study the influence of age and sex on the duration of action and metabolism of ketamine, groups of six rats of both sexes, ranging in age from one to 16 weeks were injected intraperitoneally with ketamine hydrochloride (75 mg/kg). Time to loss of righting reflex (onset time) and duration of loss of the righting reflex (sleeping time) were recorded for each rat. The rats were killed by decapitation at the point of recovery, and blood samples were collected for assay of plasma concentrations of ketamine, its *n*-demethylated metabolite (I), and the subsequent oxidation product (II), as previously described (Livingston & Waterman, 1976).

There was a significant increase in onset time from 1 to 6 weeks of age in both sexes, but after this it did not alter significantly. Sleeping time decreased markedly with increasing age from 1 to 4 weeks, in both males (97.2 to 24.1 min) and females (90.1 to 30.0 min) but thereafter it did not vary significantly. The females tended to show a longer sleeping time than the males from 4 weeks old onwards but the difference was only statistically significant in the 16 week old age group.

In the male rats the concentration of ketamine in the plasma at recovery was 4.1 ± 0.39 μg/ml in the 1 week old rats, falling to 2.67 ± 0.25 μg/ml at 6 weeks, after which it remained close to this level. Metabolite I levels followed the same pattern (2.27 ± 0.26 μg/ml at 1 week to 1.27 ± 0.17 μg/ml at 6 weeks), but no metabolite II was detected in the plasma until 3 weeks, the concentration then rose steadily with age to 6 weeks when it reached 1.25 ± 0.19 μg/ml. The changes in plasma levels of ketamine and its metabolites in the female rats followed the same pattern as the males, but the concentrations of ketamine and metabolite I were always higher than in the males of corresponding age, whilst the levels of metabolite II were always lower.

The data suggest that the decreasing sensitivity to the actions of ketamine, as demonstrated by a decrease in sleeping time from 1 to 4 weeks of age, is related to the appearance of the second metabolite in the plasma. In addition, there appears to be a sex difference in the duration of action of the drug which may be related to the difference in the ability of the sexes to produce metabolite II. These results indicate that, in the rat, the second (oxidative) step may be the rate limiting one in the degradation of this drug.

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