Effects of repeated doses of ketamine on sleeping times in rats

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Douglas & Dagirmanjian (1975) reported that repeated doses of ketamine at four day intervals produced tolerance in rats, exhibited as a decrease in sleeping time. In the experiments reported here, 25 male rats, initial body weight 88–135 g, were injected with ketamine (75 mg/kg i.p.) every fourth day for sixteen. The table also shows the plasma levels of ketamine and its metabolites at recovery and the significant fall in ketamine levels found appears to be balanced by the significant rise in metabolite II levels. The presence of relatively high levels of metabolite II directly contrasts with the results of Cohen, Chan, Way & Trevor (1973) and Cohen & Trevor (1974) who could find no evidence of this metabolite either *in vivo* or *in vitro* in rats.

A significant decrease in sleeping time in rats following repeated i.p. injections of ketamine could not be clearly demonstrated, but the presence of the cyclohexanone oxidation product has been demonstrated and its increase during the course of the

Table 1 Effects of repeated i.p. doses of ketamine (75 mg/kg) on rats (means ± s.e. mean)

Days	Sleeping time (min)	Plasma levels at recovery (5 animals) (μg/ml) Ketamine	Met. I	Met. II
1	16.60 ± 1.88 (25)	2.15 ± 0.23	0.93 ± 0.19	0.69 ± 0.11
4	18.97 ± 1.60 (20)	1.83 ± 0.06	0.90 ± 0.04	0.77 ± 0.08
8	18.94 ± 2.61 (15)	1.69 ± 0.25	0.83 ± 0.02	0.95 ± 0.08
12	14.76 ± 3.33 (10)	*1.46 ± 0.08	0.86 ± 0.05	*1.00 ± 0.05
16	8.40 ± 4.40 (5)	*1.35 ± 0.14	0.85 ± 0.02	0.80 ± 0.03

Number of rats in parentheses.
* Values significantly different from day 1 ($P < 0.05$).

sixteen days. After each dose the sleeping time was measured as the time elapsed between the loss and regaining of the righting reflex and 5 rats were killed by decapitation at the point of recovery. Mixed venous and arterial blood samples were collected in heparinized tubes, and centrifuged to obtain plasma which was then frozen for assay. The samples were extracted and assayed for ketamine and its metabolites by gas-liquid chromatography according to the method of Chang & Glazko (1972). Standard solutions of ketamine, its *n*-demethylated metabolite (I) and the subsequent oxidation product (II) were used to produce standard assay curves.

Unlike the findings of Douglas & Dagirmanjian (1975) there was no significant decrease in mean sleeping times with repeated doses (Table 1), although there was a tendency for them to decrease by day

experiments suggests that induction of the enzyme responsible for this degradation may have occurred.

References

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