Effects of bile duct ligation on ketamine anaesthesia in the rat

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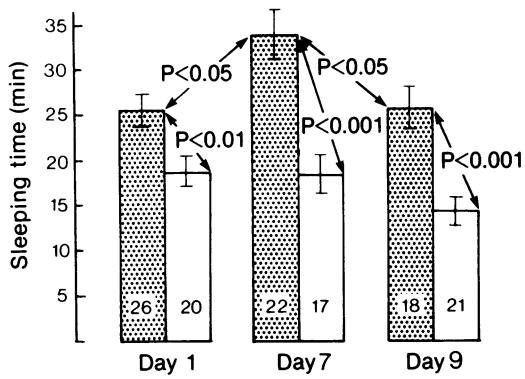
It has been suggested that hepatic metabolism plays an important part in the termination of the effects of ketamine anaesthesia (Livingston & Waterman, 1977) and the present studies were performed to examine the effects of hepatic damage induced by bile duct ligation on ketamine sleeping time in rats.

Adult male Wistar rats (225–300 g) were divided into control and experimental groups. The experimental rats had their bile ducts ligated under halothane anaesthesia whilst the control group were sham operated without ligation of the bile duct. At 2 h, 7 days and 9 days post operatively the rats were given an intraperitoneal injection of ketamine (75 mg/kg) and the sleeping time was measured as the time between loss and regaining of the righting reflex.

After the 9 day experiment the rats were decapitated at the point of recovery and blood samples collected. Ketamine and metabolite levels were measured as described previously (Livingston & Waterman, 1976). The levels of the anaesthetic and its metabolites at this time were as follows:
Ligated animals: ketamine 6.60 ± 0.46 μg/ml plasma, metabolite I 2.49 ± 0.20 μg/ml and metabolite II 1.50 ± 0.15 μg/ml. Control animals: ketamine 4.71 ± 0.37 μg/ml, metabolite I 2.46 ± 0.32 μg/ml and metabolite II 1.85 ± 0.14 μg/ml. The levels for ketamine were significantly higher in the ligated group ($P < 0.01$) whilst the levels of metabolites I and II were not significantly altered.

The results for the effects of bile duct ligation on sleeping times are shown in Figure 1 and it can be seen that they showed a significant rise in the ligated animals at all three time points, and whilst this is not surprising in the seven and nine day post-operation animals, since post-mortem examination showed considerable liver damage, and we have proposed that liver metabolism is a major factor in the termination of the effect of ketamine, the signficant rise in sleeping time two hours after bile duct ligation may indicate the possibility of bilary excretion of this drug as a factor in the termination of its action.



Sleeping time following 75 mg/kg LP. Ketamine.
▨ Bile duct ligated, □ Sham operated.

Figure 1

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Behavioural changes induced by olfactory bulb ablation and intrabulbar injection of 5,6-DHT: susceptibility to psychotropic drugs

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We have established that antidepressant drugs selectively reverse the effects of bilateral olfactory bulb ablation (van Riezen, Schnieden & Wren, 1977; Cairncross, Cox, Forster & Wren, 1977a) and have recently demonstrated that bilateral intrabulb injection of 5,6-dihydroxytryptamine (5,6-DHT, 8μg) produces similar behavioural and biochemical effects to bulbectomy (Cairncross, Cox, Forster & Wren, 1977b). We have now attempted to assess the susceptibility of the 5,6-DHT-induced syndrome to alteration by psychotropic drugs.

The antidepressant drugs amitriptyline (5 mg/kg) and mianserin (5 mg/kg) caused a significant reversal of both the behavioural and biochemical effects of bulbectomy and 5,6-DHT injection (Table 1). However, these drugs had no effect on either the behaviour or the plasma 11-hydroxycorticosterone (11-OHCS) concentration of sham operated and vehicle injected rats. Amphetamine, chlorpromazine and chlordiazepoxide altered the behaviour and the 11-OHCS concentrations of 5,6-DHT treated rats in a manner very similar to their effects on bulbectomized rats. Thus the 5,6-DHT injected rat appears to selec-

tively predict drugs with antidepressant activity in a manner analagous to that of the bulbectomized rat.

Cryostat sections of fixed brains were stained according to the Hjorth-Simonsen (1970) modification of the Fink-Heimer (1967) method for visualizing nervous degeneration. 5,6-DHT caused a spread of degenerating terminals and fibres from the injection site, which collected into the medial and lateral olfactory tracts. Degeneration was also traced to the olfactory tubercle, pyriform cortex asnd the medial amygdaloid area.

The ability of noradrenaline, dopamine and 5-hydroxytryptamine to stimulate the production of 3,5-cyclic AMP in olfactory bulb slices (250 × 250 μM) was assessed using a protein binding assay (Radiochemical Centre Amersham). Only noradrenaline caused a significant increase in 3,5-cyclic AMP formation.

Table 1 Effects of chronic psychotropic drug treatment on behaviour and plasma 11-OHCS concentration in bulbectomized and 5,6-DHT treated rats[1]

Treatment	*Dose (mg/kg)*	*Passive avoidance[2] (N° of trials)*	*Irritability[2] (Score)*	*Resting 11-OHCS[2] (μg/100ml plasma)*
Bulbectomy (OB)	—	6.8 ± 0.9	5.4 ± 0.4	42.8 ± 4.4
Sham operation	—	3.6 ± 0.2	2,4 ± 0.6	18.5 ± 1.3
5,6-DHT 8μg	—	6.1 ± 0.6	4.9 ± 0.2	36.6 ± 2.3
Vehicle[3]	—	3.6 ± 0.5	1.6 ± 0.5	13.6 ± 1.0
OB+amitriptyline	5	3.6 ± 0.7*	1.4 ± 0.5*	19.6 ± 2.4*
OB+mianserin	5	2.4 ± 1.0*	2.6 ± 0.7*	22.7 ± 2.3*
OB+amphetamine	1	8.2 ± 0.6	5.0 ± 0.3	37.1 ± 4.6
OB+chlorpromazine	1	7.1 ± 0.7	0.7 ± 0.3*	17.2 ± 5.0*
OB+chlordiazepoxide	5	6.0 ± 0.5	1.9 ± 0.4*	21.8 ± 1.8*
DHT+amitriptyline	5	4.7 ± 0.5*	2.3 ± 0.2*	21.6 ± 3.1*
DHT+mianserin	5	3.8 ± 0.5*	2.1 ± 0.3*	24.6 ± 1.3*
DHT+amphetamine	1	7.0 ± 0.6	4.8 ± 0.8	45.2 ± 4.5
DHT+chlorpromazine	1	5.4 ± 0.4	1.5 ± 0.4*	13.7 ± 1.1*
DHT+chlordiazepoxide	5	6.5 ± 0.7	1.5 ± 0.5*	19.1 ± 1.0*

1 Chronic drug treatment began 14 days after surgery. Behavioural tests were performed after a minimum of 7 days treatment.
2 Results expressed as mean ± s.e. mean for between 8 and 16 rats.
3 2% ascorbic acid in 0.9% NaCl solution.
* Results which are significantly different ($P<0.05$) from appropriate control.

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