Table 1 Effects of etorphine, acepromazine and diprenorphine on cardiovascular function

Time (min)	*Heart rate (beats/min)*	*Stroke volume (ml kg^{-1})*	*Cardiac output (ml kg^{-1} min^{-1})*	*T P R (dyn s cm^{-5})*	*M A P (mm Hg)*	*Hb concentration (g/100 ml)*
control	42 ± 2	1.66 ± 0.07	66 ± 3	656 ± 41	123 ± 3	11.7 ± 0.3
E + 5	134 ± 10**	0.77 ± 0.07**	102 ± 13**	608 ± 65	161 ± 8**	14.5 ± 0.3**
E + 15	117 ± 8**	0.76 ± 0.04**	87 ± 6**	474 ± 44**	117 ± 7	13.3 ± 0.3**
E + 30	122 ± 12**	0.83 ± 0.11**	93 ± 7**	503 ± 62**	126 ± 6	12.7 ± 0.3
D + 5	93 ± 12**	1.03 ± 0.07**	91 ± 10*	426 ± 60**	96 ± 4**	12.0 ± 0.4
D + 15	66 ± 6**	1.23 ± 0.08**	77 ± 6	434 ± 48**	90 ± 4**	10.7 ± 0.3**
D + 30	52 ± 4*	1.32 ± 0.07**	66 ± 5	546 ± 59*	90 ± 5**	9.8 ± 0.2**
D + 60	47 ± 3	1.37 ± 0.07**	62 ± 3	539 ± 50**	93 ± 4**	9.3 ± 0.2**

Values are means ± s.e. mean for twelve ponies. Times refer to the i.v. administration of etorphine and acepromazine (*E*) or the i.v. injection of diprenorphine (*D*). The significance of differences from control values was assessed by paired *t*-tests and is indicated by asterisks: *, $P < 0.05$; **, $P < 0.01$.

arterial blood pressure (MAP) and arterial HB concentration were increased after 5 min but had returned to the control ranges by 15 min (MAP) and 30 min (Hb concentration). Total peripheral resistance (TPR) was initially unchanged and then reduced at 15 and 30 minutes. Following diprenorphine administration, TPR decreased further and MAP and Hb concentration also fell below control levels, while heart rate and cardiac output initially remained above controls before returning to the normal ranges by 60 and 15 min, respectively.

It is concluded that etorphine causes sympathoadrenal stimulation as a result of its respiratory depressant effects (Hillidge & Lees, 1975) and possibly by other mechanisms and that some of the sympathetic effects are partially offset by an α-adrenoceptor blocking action of acepromazine. This action of acepromazine probably accounted also for the reductions in MAP, TPR and Hb concentration which occurred after the actions of etorphine had been antagonized with diprenorphine.

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The effect of inhibitors of alcohol metabolism on the changes in the hepatic microsomal metabolism of foreign compounds produced by a single dose of ethanol in the rat

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The administration to rats of a single oral dose of ethanol has been found to produce a selective induction of hepatic microsomal aniline hydroxylation, a decrease in aminopyrine demethylation and no change in the activity of the components of the hepatic microsomal mixed function oxidase (Powis, 1975). The present work is an attempt to distinguish between the direct effects of ethanol and the effects resulting from the metabolism of the ethanol, on the hepatic microsomal metabolism of foreign compounds.

Ethanol or acetaldehyde were administered to unanaesthetized rats by stomach tube and inhibitors of alcohol and aldehyde dehydrogenase were administered by i.p. injection. The hepatic microsomal fraction was prepared, 24 h after the administration of the various compounds, by the method of Ernster, Siekevitz & Palade (1962) in 0.25 M sucrose containing 0.05 M Tris buffer pH 7.4. The metabolism of foreign compounds was measured over 30 min at 37°C using the

incubation conditions described by Mazel (1971). The formation of *p*-aminophenol from aniline was measured by the method of Schenkman, Remmer & Estabrook (1967) and formaldehyde formed from aminopyrine by the method of Nash (1953). Microsomal protein was measured by the method of Lowry, Rosebrough, Farr & Randall (1951).

Acetaldehyde oxime (200 mg/kg), an inhibitor of alcohol dehydrogenase (Lester & Benson, 1970), itself produced no significant change in aniline hydroxylation but caused an increase in aniline hydroxylation in rats fed ethanol (85 mmol/kg) from 9.4 ± 0.4 (mean ± s.e. mean) to 21.9 ± 1.3 nmol mg^{-1} 30 min^{-1} ($n = 6$, $P < 0.01$). Acetaldehyde oxime produced a decrease in aminopyrine demethylation of a similar magnitude to that caused by ethanol itself although there was no additive effect when both compounds were administered together. Pyrazole (200 mg/kg), also an inhibitor of alcohol dehydrogenase (Goldberg & Rydberg, 1969), produced an increase in aniline hydroxylation and a decrease in aminopyrine demethylation. It had similar effects to acetaldehyde oxime, however, on the changes in metabolism produced by ethanol.

Acetaldehyde (22 mmol/kg, fed to rats 24 h and 18 h before the preparation of the microsomal fraction) had no effect upon aniline hydroxylation but produced a decrease in aminopyrine demethylation from 105.3 ± 5.8 to 75.5 ± 5.3 nmol mg^{-1} 30 min^{-1} ($n = 6$, $P < 0.01$). Disulphiram (300 mg/kg), an inhibitor of aldehyde dehydrogenase (Dietrich & Erwin, 1971), reduced aminopyrine demethylation to 70.9 ± 3.6 nmol mg^{-1} 30 min^{-1} ($n = 6$, $P < 0.01$) but also potentiated the decrease in aminopyrine demethylation in rats fed only half the previous dose of acetaldehyde to 37.9 ± 5.1 nmol mg^{-1} 30 min^{-1} ($n = 6$, $P < 0.05$).

It is concluded from these results that the increase in aniline hydroxylation produced by the administration of a single dose of ethanol is a consequence of the ethanol itself, whilst the decrease in aminopyrine demethylation is a consequence of the metabolism of ethanol to acetaldehyde.

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Catecholamine metabolism and liver dysfunction during induction of ethanol dependence

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We have reported that concentrations of noradrenaline and dopamine increase in brain during the induction of ethanol dependence in mice (Griffiths, Littleton & Ortiz, 1974). These changes can be demonstrated to be an important factor in the induction of dependence, and their cause is of interest. The experiments reported here suggest a possible mechanism.

We have induced ethanol dependence in TO strain, white mice as described previously (Griffiths *et al.*, 1974). Mice were killed at intervals during chronic ethanol administration by whole body immersion in liquid nitrogen, brain concentrations of amino acids estimated (modified gas-liquid chromatographic method of Islam and Darbre, 1969) and livers taken for estimation of triglycerides (methods of Folch, Lees & Sloane Stanley, 1957; Van Handel & Zilversmit, 1957). In parallel experiments mice were withdrawn daily