Rapid development of cellular tolerance during continuous administration of ethanol to mice by inhalation

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Investigation of the time course of development of cellular tolerance to ethanol requires the maintenance of high concentrations of the drug in the bloodstream. Commonly used laboratory animals metabolize ethanol rapidly, making it difficult to achieve these conditions with conventional routes of administration. The following experiments overcome these problems by administration of ethanol to mice by inhalation.

Male TO mice (20–25 g) were exposed to ethanol vapour (30 mg/l) in a chamber (see Griffiths, Littleton & Ortiz, 1974) modified to allow manipulation within, and containing a rotating rod (2 cm in dia., 0.5 Hz). In separate experiments mice were tested repeatedly for loss of righting reflex or loss of rotarod balance. Immediately an animal was unable to perform the test it was removed for estimation of blood ethanol concentration (see below). After 30 min the mouse was again placed in the inhalation chamber and testing recommenced. This cycle of testing, removal, blood ethanol measurement and replacement continued for 8 hours.

Three measurements of ethanol in expired air were taken (see Abu Murad, Begg, Griffiths & Littleton, 1977) 15 and 30 min after removal of an animal from the chamber. The means of these values were converted to give concentrations of ethanol in blood, and extrapolated to give the blood ethanol concentration on loss of performance in the chamber.

Results, shown in the figure, demonstrate that cellular tolerance to ethanol develops rapidly and may reach a maximum, in which approximately double the concentration of ethanol is required to produce the behavioural end-point, after as little as 5 hours. This confirms and extends suggestions made by Leblanc, Kalant & Gibbins (1975) based on acute administration of ethanol to rats. Tolerance to ethanol may

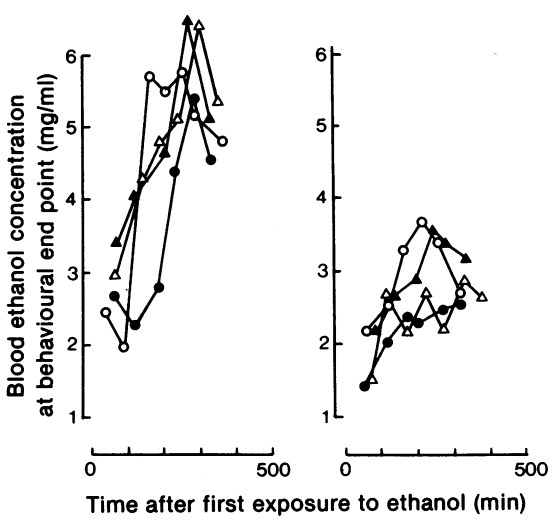

Figure 1 Development of cellular tolerance to ethanol. The figure shows the concentration of ethanol in blood at which loss of righting reflex (left) or (separate experiments, on right) loss of rotarod balance occurs in mice during subacute exposure to ethanol vapour. Connected symbols represent values obtained for an individual mouse. Blood ethanol concentrations at which loss of performance first occurred were: righting reflex 2.9 ± 0.2 mg/ml, rotarod balance 1.8 ± 0.2 mg/ml (means ± s.e.mean, $n = 4$). For further details see text.

therefore develop as rapidly as that to other centrally acting drugs including opiates.

In subsequent experiments using these techniques we observe significant differences in the rate and magnitude of development of cellular tolerance to ethanol of mice of different age and strain. We intend to use these differences to investigate the biochemical basis of cellular tolerance.

These experiments were supported by grants from the Mental Health Foundation and the Medical Council on Alcoholism.

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The effects of (−)-isoprenaline, salbutamol and nylidrin on gastric acid secretion in conscious dogs with Heidenhain pouches

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β-Adrenoceptor agonists such as (−)-isoprenaline and salbutamol are potent inhibitors of pentagastrin-induced gastric acid secretion in the dog (Curwain, Holton & Spencer, 1972; Daly & Stables, 1977). However, histamine-induced secretion is reported to be unaffected by salbutamol, enhanced by low doses of isoprenaline and inhibited by high doses of isoprenaline (Curwain *et al.*, 1972). We have reinvestigated the effects of (−)-isoprenaline and salbutamol on gastric secretion and have also studied nylidrin, a β-adrenoceptor agonist claimed to stimulate gastric secretion (Geumei, Issa, El-Gindi & Abd-el-Samie, 1969).

Three male beagle dogs (13–18 kg) with well-established Heidenhain pouches were used. Submaximal gastric acid secretion was induced by continuous intravenous infusion of pentagastrin (1–4 μg kg^{-1} h^{-1})

Table 1 The effects of β-adrenoceptor agonists on gastric secretion induced by pentagastrin or histamine in conscious dogs with Heidenhain pouches

Secretory stimulant and β-adrenoceptor agonist	*n*	*Increased secretion*			*Decreased secretion*
		Incidence†	*Dose (ng kg^{-1} min^{-1})*	*% Increase**	*ED_{50} ± s.e.mean (effective dose range ng kg^{-1} min^{-1})*
versus pentagastrin					
(−)-Isoprenaline	30	0			5.7 ± 2.7 (1–10)
Salbutamol	27	0			82.4 ± 23.9 (30–300)
Nylidrin	12	1	300	40	999 ± 74 (300–3,000)
versus histamine					
(−)-Isoprenaline	15	2	100	96, 15	299 ± 105 (100–1,000)
Salbutamol	12	1	30	8	514 ± 84
		1	300	11	(300–1,000)
Nylidrin	9	3	300	10, 11, 17	11,500 ± 3,145 (3,000–10,000)

n = number of experiments.
† = incidence in 3 experiments at dose level shown.
* = values given are all significant by *t* test at $P < 0.05$.