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BIOGENIC AMINES AND HEAD TWITCHES IN MICE DURING ETHANOL WITHDRAWAL

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After chronic administration of ethanol to mice by the intragastric route head twitches occur as part of the ethanol withdrawal syndrome. Treatments which reduce brain 5-hydroxytryptamine or increase brain noradrenaline inhibited ethanol withdrawal head twitches, whereas treatments which increase brain 5-hydroxytryptamine or reduce brain noradrenaline were capable of inducing head twitches in control animals.

Head twitches have been described as a consistent response in mice after withdrawal of ethanol administered either in vapour form or by the intragastric route (Hammond & Schneider, 1973). Similar head twitches in mice are also produced by drugs which are known hallucinogens in man (Corne & Pickering, 1967). Since hallucinations are a frequent symptom of ethanol withdrawal in man (Victor, 1973) head twitches may reflect this aspect of ethanol withdrawal in the mouse. The mechanism of production of head twitches after termination of oral ethanol administration has been investigated by the use of drugs that interfere with the action of or synthesis of 5-hydroxytryptamine or noradrenaline.

Methods Ethanol was administered for 4 days to male T/0 mice using an intragastric dosage schedule (Hammond & Schneider, 1973). The effect of drugs was assessed at the peak time of incidence of head twitching, 24 h after the last ethanol dose. The drugs administered were as follows.

(1) Drugs affecting central 5-hydroxytryptamine metabolism: *p*-chlorophenylalanine methyl ester hydrochloride (Pfizer), (±)-*p*-chloroamphetamine hydrochloride (Regis Chemical Co), methergoline (Liserdol-Farmitalia), methysergide bimaleate (Sandoz) and 5-hydroxy-DL-tryptophan (Sigma).
(2) Drugs affecting central noradrenaline metabolism: α-methyl-*p*-tyrosine (Sigma), noradrenaline hydrochloride (Sigma), (+)-amphetamine sulphate (May and Baker Ltd).

For oral administration drugs were dissolved in water or suspended in 10% gum acacia. Drugs administered intraperitoneally or subcutaneously were dissolved in 0.9% w/v NaCl solution (saline). Methergoline was dissolved in 1% w/v ascorbic acid. Vehicle was administered to controls.

Intracerebral injections were made by the method of Haley & McCormick (1957), the noradrenaline being dissolved in sterile saline. Each mouse received 0.05 ml. In experiments where antagonists of the ethanol withdrawal head-twitch were tested, the dose of test drug that reduced the head-twitch incidence to 50% that of control levels (ED_{50}) was determined on a quantal basis using logit analysis. In experiments where only a reduction in head-twitch incidence was observed the Mann Whitney U test was used to determine the statistical significance.

Results *p*-Chlorophenylalanine (200 mg/kg, i.p.) and *p*-chloroamphetamine (20 mg/kg, i.p.), both inhibitors of 5-hydroxytryptamine biosynthesis, reduced head-twitches occurring during ethanol withdrawal. Centrally acting antagonists of 5-hydroxytryptamine, methergoline (Mawson & Whittington, 1970) and methysergide also reduced head-twitches when administered one hour before peak withdrawal.

Noradrenaline administered into the cerebral ventricles or amphetamine administered subcutaneously markedly inhibited ethanol withdrawal head-twitches. These results are shown in Table 1.

Similar head-twitches to those observed in ethanol withdrawal were seen 6 h after α-methyl-*p*-tyrosine (200 mg/kg, i.p.) or 15-19 min after 5-hydroxytryptamine (400 mg/kg, i.p.). All three types of head-twitch were suppressed by methergoline (4 mg/kg, i.p.) or noradrenaline (5 μg intracerebroventricularly).

Discussion Head-twitches associated with ethanol withdrawal in mice were inhibited by treatments which decreased brain 5-hydroxytryptamine or increased brain noradrenaline. Conversely, treatments which decreased brain noradrenaline or increased brain 5-hydroxytryptamine were capable of inducing head-twitches in control animals.

These findings further illustrate the complicated relationship between brain neurotransmitters and different behavioural aspects of the ethanol

Table 1 Compounds inhibiting head-twitches associated with ethanol withdrawal in mice.

Compound	*Route*	*ED_{50} value to reduce head-twitches (mg/kg)*	*95% fiducial limits (mg/kg)*
Ethanol	Oral	3990	(2610–6410)
Methergoline	Oral	1.8	(1.15–2.69)
Methergoline	s.c.	0.4	(0.12–1.7)
Methysergide	s.c.	1.27	(0.18–9.18)
Noradrenaline	i.c.v.	0.1	(N.A.)
Amphetamine	s.c.	7.18	(4.8–10.8)

All drugs given one hour before observation except noradrenaline (35 min).
Doses were administered orally, subcutaneously (s.c.) or intracerebroventricularly (i.c.v.).
N.A. = not available.

withdrawal syndrome. For example, Griffiths, Littleton & Ortiz (1974a;b) have demonstrated that inhibition of catecholamine synthesis inhibits the initial locomotor excitement but potentiates the associated convulsive state, whereas inhibition of 5-hydroxytryptamine synthesis does not appear to affect these aspects of ethanol withdrawal. In addition, the work of Goldstein (1973) suggests that γ-aminobutyric acid plays some part in ethanol withdrawal convulsions.

Our results lead to the proposition that head-twitches associated with ethanol withdrawal could be the result of changes in the relative levels of noradrenaline and 5-hydroxytryptamine in the brain.

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