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A simple screening test for drugs of potential use in ethanol withdrawal

Recently, models for ethanol dependence utilizing mice have been described and these are obviously of interest as screening tests for drugs which may be useful in the treatment of alcohol withdrawal. The administration of ethanol for several days followed by its withdrawal is associated with a characteristic syndrome (Freund, 1969; Goldstein & Pal, 1971; Griffiths, Littleton & Ortiz, 1973) which can be scored for severity in the way described by Goldstein (1972a). Many drugs which are currently used in therapy of ethanol withdrawal states also show effects in the animal model of withdrawal similar to those seen in the clinical condition (Goldstein, 1972b). We now wish to report that the acute administration of acetaldehyde to mice is associated with a transient behavioural change which shares many characteristics with the ethanol withdrawal syndrome and that this may serve as an alternative simple screening test.

The ethanol withdrawal syndrome in mice includes tremor, piloerection and convulsions on handling the animals. All these signs are shown after the injection of acetaldehyde (200 mg kg^{-1} i.p.) as illustrated in Fig. 1a. The peak intensity of ethanol withdrawal signs in mice occurs at a time when blood and brain ethanol concentrations are very low, similarly these aspects of the behavioural change after acetaldehyde occur at a time when blood and brain acetaldehyde concentrations have fallen to low levels (Fig. 1b).

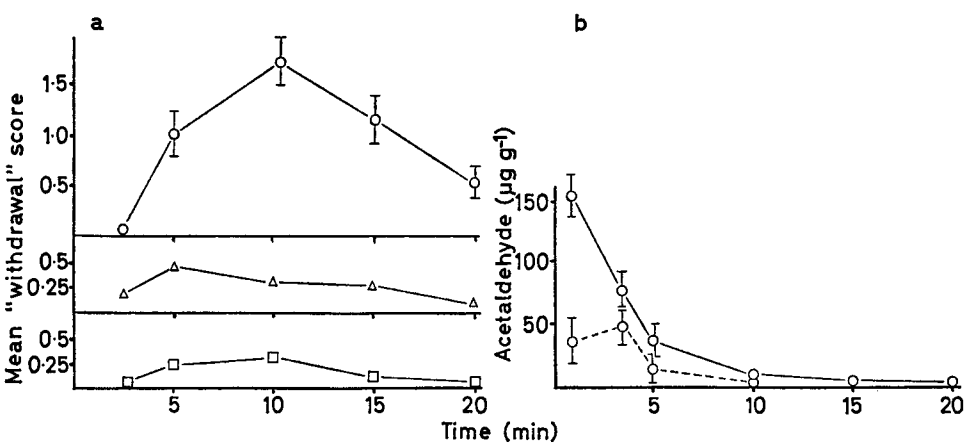

FIG. 1. (a) Behavioural change in mice after the administration of acetaldehyde (200 mg kg^{-1} i.p.). Male white mice (18–20 g) were used and the behavioural change was assessed in the way described by Goldstein & Pal (1971) and Goldstein (1971) ○, Handling convulsions; △, piloerection; □, tremor. Each point represents the mean score of 20 mice. Vertical bars represent standard errors.

(b) Blood and brain acetaldehyde concentrations in mice after the administration of acetaldehyde (200 mg kg^{-1} i.p.). Blood concentration (solid lines) and brain concentration (dotted lines) were measured in the way described by Griffiths & others (1974). Vertical bars represent standard errors of the mean of at least 5 determinations.

Table 1. *A comparison of the effect of drugs on acetaldehyde-induced convulsions and ethanol withdrawal convulsions.* A minimum of ten mice were used for each drug administration. Convulsions were scored in the way described by Goldstein (1972a). "Time" in the "Pretreatment" column refers to the time before acetaldehyde injection at which the pretreatment was given.

Pretreatment drug	Dose mg kg^{-1} i.p.	Time	Acetaldehyde convulsions	Ethanol withdrawal convulsions (Goldstein, 1972b, 1973)
Ethanol	2000	15′	completely suppressed	completely suppressed
Phenobarbitone	50	2 h	completely suppressed	completely suppressed
Pentobarbitone	50	30′	marked reduction	completely suppressed
Chlordiazepoxide	20	15′	marked reduction	completely suppressed
Diazepam	5	15′	completely suppressed	completely suppressed
Chlorpromazine	10	15′	slight increase	increase
Propranolol	20	30′	increase	increase (50 mg kg^{-1})
Phentolamine	20	30′	increase	increase
Reserpine	5	4 h	increase	marked increase
α-Methyl tyrosine methylester	400	4 h	increase	slight increase (2 × 100 mg kg^{-1})
Nialamide	50	2 h	slight reduction	no effect
p-Chlorphenylalanine	300	8 h	no effect	no effect

The convulsions on handling are thought to be the most important sign of ethanol withdrawal in mice and this sign has been used by Goldstein (1972b, 1973) to assess the effect of drugs during ethanol withdrawal. In Table 1, the ability of a number of drugs to modify acetaldehyde induced convulsions is compared with the results obtained by Goldstein.

The drugs tested had qualitatively similar actions on acetaldehyde-induced convulsions and ethanol withdrawal convulsions. This may represent a non-specific effect of these drugs on convulsions, but if the other signs (e.g. tremor, piloerection) are included, it is thought that acetaldehyde injection to mice may serve as a simple initial screening test for drugs with a potential use in ethanol withdrawal. The implications of this work for a possible involvement in ethanol dependence of acetaldehyde derived from ethanol will be discussed in a later paper. The financial support of the Medical Council on Alcoholism is gratefully acknowledged.

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