Ethanol behaves as an NMDA antagonist with respect to locomotor stimulation in monoamine-depleted mice

Rapid Communication

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Summary. Previous studies have shown that administration of NMDA antagonists in combination with the α2-adrenoceptor agonist clonidine results in a marked locomotor stimulation in monoamine-depleted mice, albeit the pattern of movement produced is highly stereotyped and primitive. Ethanol has recently been suggested to display NMDA antagonistic properties; hence, in the present study the ability of ethanol to produce locomotor activation in monoamine-depleted mice with a movement pattern similar to that produced by NMDA antagonists was investigated. It was found that neither ethanol nor clonidine given alone reversed the akinesia induced by pretreatment with reserpine (10 mg/kg; 18 h) and α-methyl-para-tyrosine (500 mg/kg; 2 h). However, when the drugs were combined a marked stimulatory effect was observed and, indeed, the animals displayed the same primitive locomotor pattern previously observed following treatment with NMDA antagonists in conjunction with clonidine. The locomotor response was effectively blocked by pretreatment with the selective α2-adrenoceptor antagonists yohimbine (10 mg/kg) or idazoxan (10 mg/kg) but not with the selective α1-adrenoceptor antagonist prazosin (1 mg/kg). The present results suggest that ethanol in conjunction with α2-adrenoceptor stimulation induces locomotion in monoamine-depleted mice via a mechanism that may involve interference with glutamate receptor-mediated neurotransmission.

Keywords: Ethanol, NMDA receptor, catecholamines, clonidine, locomotor activity.

Introduction

Accumulating evidence, obtained by a variety of different methodological approaches, suggests that ethanol interferes with excitatory amino acid neuro-
transmission. Electrophysiological studies have revealed that ethanol inhibits N-methyl-D-aspartate (NMDA) activated ion currents in hippocampal slices in vitro (Lima-Landman and Albuquerque, 1989; Lovinger et al., 1989) and attenuates the in vivo response of central noradrenergic neurons to microiontophoretically applied NMDA or quisqualate (Engberg and Hajos, 1992). Furthermore, ethanol is able to inhibit NMDA-stimulated release of noradrenaline from rat cortical slices (Göthert and Fink, 1989), and behavioural experiments have shown that NMDA antagonists are able to reduce alcohol withdrawal symptoms, such as seizures (Grant et al., 1990; Morisset et al., 1990).

Previous behavioural studies have shown that treatment with NMDA antagonists in combination with the α2-adrenoceptor agonist clonidine produces marked locomotor stimulation in monoamine-depleted mice (see Carlsson et al., 1991). The pattern of locomotion achieved with this treatment is highly stereotyped and consists of a constant-speed forward locomotion; the animals cannot turn when reaching a corner and they do not display any other type of behaviour, such as grooming, jumping or climbing. This behavioural pattern is typically observed in monoamine-depleted mice receiving an NMDA antagonist (in combination with clonidine) and may prove a valuable behavioural model to identify drugs with NMDA antagonistic properties.

The aim of the present study was to determine whether ethanol in monoamine-depleted mice is able to induce locomotor activity, with a pattern characteristic of NMDA antagonists.

Methods

Male albino mice of the NMRI strain (20–30 g) were purchased from ALAB, Sollentuna. Reserpine (CIBA-GEIGY), yohimbine HCl (Sigma), and prazosin HCl (Pfizer) were dissolved in a few drops of glacial acetic acid and 5.5% glucose solution. Idazoxan (Reckitt & Colman) was dissolved in distilled water. α-Methyl-para-tyrosine methylester HCl (α-MT; Sigma) and clonidine HCl (Boehringer Ingelheim) were dissolved in physiological saline. All drugs were dissolved in an ultrasonic bath and injected i.p. in a volume of 10 ml/kg, with the exception of reserpine which was given in a volume of 20 ml/kg. Appropriate vehicle treatment was always given so that all mice in one and the same experiment received the same injection volumes. Doses are given in the figure legends and refer to the salts of the drugs.

Locomotor activity was registered in a circular track by means of IR detectors as previously described (see Carlsson et al., 1991). All animals in this study received reserpine (10 mg/kg i.p.) 18 h prior to the acute experiment. One hour following reserpine administration and throughout the experiment the ambient temperature was held at 26°C. In addition, the animals were kept warm on electric pads until the locomotor registration commenced.

Mann-Whitney U-test was used throughout for comparisons between groups.

Results

All mice used in the present study were depleted of monoaminergic stores by means of reserpine (10 mg/kg; 18 h) and α-MT (500 mg/kg; 2 h) pretreatment. Administration of either ethanol (2 g/kg) or clonidine (1 mg/kg) did not result