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BRIEF COMMUNICATION

Ethanol-Induced Mouse Strain Differences in Locomotor Activity

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RANDALL, C. L., J. A. CARPENTER, D. LESTER AND H. J. FRIEDMAN. *Ethanol-induced mouse strain differences in locomotor activity*. PHARMACOL. BIOCHEM. BEHAV. 3(3) 533–535, 1975. – C57BL/6J mice showed dose dependent decreases in locomotor activity with increasing IP doses of ethanol (0.0, 0.75, 1.50 and 2.25 g/kg), while BALB/cJ mice showed dose dependent increases in activity; both strains were equally active with saline. Whether this finding represents decreased CNS responsivity in C57BL mice to ethanol's excitatory effect or increased response to its depressant action at sub-hypnotic doses is unclear, since anesthetic doses produce anesthesia of far shorter duration in the C57BL strain than in the BALB strain. It is possible that the biphasic action of alcohol is under the control of separate and distinct mechanisms, rather than a common one, and that these two mechanisms are differentially affected by alcohol. Endogenous as well as ethanol-induced neurochemical differences in biogenic amines may also be correlated with the genetic variation in CNS responsivity towards alcohol.

Ethanol Locomotor activity Mouse strain differences Ethanol and CNS effects

THE existence of inbred mouse strains differing in voluntary oral consumption of an alcohol solution is well known [6, 12, 13]. When presented with a choice between 10% v/v ethanol and water, the C57BL strain consumes between 60 and 90% of its total fluid intake as alcohol, while the DBA and BALB strains drink only 5 to 10% as an alcohol solution. These particular strains have enabled investigators to examine the genetic, biochemical and pharmacological determinants of alcohol self-selection and alcohol avoidance [1, 2, 14, 18, 19, 20, 23, 24, 29].

The C57BL strain is less sensitive than the BALB strain to the anesthetic effect of alcohol as measured by sleep time [1, 7, 11, 16]. Thus C57BL mice regain the righting reflex after 4.2 g ethanol/kg in one-third the time of non-drinking BALB mice even though the rates of alcohol elimination in these two strains are essentially identical [8]. C57BL mice also require more than twice the dose of alcohol (as compared to DBA/2, BALB/c or CBA mice) to reduce the amplitude of a jaw reflex [21,22]. These studies imply a possible correlation between the amount of voluntary ethanol consumption and neural and behavioral tolerance to alcohol: the strain least affected by alcohol drinks the most [21,22]. The dosages employed in the studies cited far exceed the rate at which alcohol is voluntarily consumed by any of these strains.

MacInnes and Uphouse [10] have reported, however, the differential ethanol-induced effects of alcohol on acquisition, but not retention, of a passive avoidance task in C57BL/6, DBA/2 and F_1 hybrid mice after doses of 0.5 to 3.0 g ethanol/kg. The C57BL mice took significantly fewer traials to reach criterion than did the other two strains at 1.5, 2.0 and 2.5 g ethanol/kg, indicating their lesser sensitivity to ethanol's pharmacological action on passive avoidance acquisition at moderate doses and in concordance with the results on anesthesia duration previously reported for higher doses.

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Activity and duration of anesthesia (sleep) may reasonably be considered to form a continuum, and since strain differences in sleep have been well documented, the present study examined the effects of sub-anesthetic doses of alcohol on spontaneous locomotor activity, measured in a stabilimeter. It was hypothesized that the non-drinker BALB strain would be more affected (i.e., less active) after ethanol challenge than the C57BL strain. Our results do not support this hypothesis.

METHOD

Animals

Eight male C57BL/6J and eight male BALB/cJ mice 12 weeks of age were used. The mice were purchased from Jackson Laboratories (Bar Harbor, Maine) at approximately 6 weeks of age and housed singly in plastic cages with San-I-Cel bedding. Purina lab chow and water were available ad lib.

Apparatus

The stabilimeter cages utilized in this study have been described previously [3]. They are stainless steel wire mesh cages (8.75 X 10.0 X 18.75 cm) mounted on a central axle and able to tilt longitudinally approximately 3 mm. At one end of the cage a platinum wire makes contact with a mercury pool after a downward tilt of the cage, the switch activating a counter in another room. The cages employed were organized in groups of 6 in large wooden boxes equipped with temperature controls and with background noise produced by small exhaust fans. The cages were separated from each other by wooden partitions. Animals were assigned to the same cages throughout the experiment.

Procedure

The animals were given 3 daily 1/2 hour periods of acclimation to the stabilimeter cages before the experiment began. All testing was conducted from 0100 to 0200 hr so as to maximize activity scores. The animals were transported from the vivarium to the testing room and placed initially in a randomly assigned stabilimeter cage and allowed a 15 min baseline period; they were then removed from their cages and injected intraperitoneally (0.02 ml/g) with either 0.9% saline (zero alcohol dose) or ethanol in 0.9% saline at doses of 0.75, 1.50 and 2.25 g/kg. The animals were immediately returned to their cages and their activity measured for a 1 hr period. The experimental design employed four 4 X 4 Latin Squares, two for each strain, all animals receiving each of the 4 doses of alcohol (0.0 to 2.25 g/kg) in a predetermined sequence governed by the particular Latin Square. Three days separated each injection.

RESULTS

A graphical and visual examination of the data suggested transformation to log activity scores. The 2 strains were found to have homogeneous Within Group variance ($F_{max} = 1.42$, $df = 7$, ns); Strains were significantly different ($F = 5.50$, $df = 1$, $p<0.05$). Alcohol Dose was not significant, but Alcohol Dose X Strains was significant ($F = 4.11$, $df = 3$, $p<0.025$). A partition of Alcohol Dose X Strains into trends showed the Alcohol Dose Linear X Strains interaction to be highly significant ($F = 11.36$, $df = 1$, $p<0.005$). The response of the 2 strains to the alcohol doses yielded non-parallel linear dose-response functions (Fig. 1) with 92% of the Alcohol X Strains interaction occurring in this one partition. Analysis of each strain alone showed the trend over doses for the C57BL to be significant ($F = 6.95$, $df = 1$, $p<0.025$), with a negative slope, while the trend for the BALB strain was also significant ($F = 4.80$, $df = 1$, $p<0.05$), but with a slight positive slope. Thus, as illustrated in Fig. 1, the C57BL mice decreased their activity while the BALB mice increased their activity as the alcohol dose increased. No strain difference in activity was evident with the zero dose of alcohol (saline).

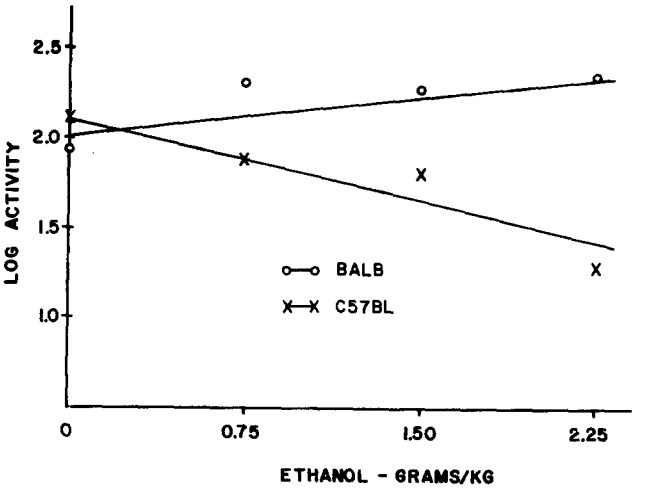

FIG. 1. Mean log activity scores of C57BL/6J and BALB/cJ mice as a function of alcohol dosage (g/kg).

DISCUSSION

The present study is the second demonstration of strain differences in the effect of alcohol on locomotor activity in inbred mouse strains, but the present study circumvents the major criticism of McClearn's study [11] by administering alcohol in a specified dose rather than by the inhalation of what can only be inconsistent doses of alcohol vapor. Nonetheless, both studies show differential alcohol-induced effects on activity in the C57BL and BALB strains and in both activity scores are lower in the C57BL strain.

The observed increase in activity in the BALB strain at low and moderate doses of alcohol is not necessarily inconsistent with the notion of greater sensitivity to alcohol in this strain [7, 11, 16]. Ataxia, random stumbling, as well as other such behaviors, are commonly noted after alcohol administration and could result in an increased number of cage tilts. Because of apparatus limitations, behavioral observations were, unfortunately, not possible during the testing situation. The fact that BALB and C57BL mice were equally active at the zero alcohol dose should be emphasized, for, under other test conditions, BALB mice are either less or more active and more "emotional" than C57BL mice [27]. Task specificity obviously deserves attention.

The biphasic action of alcohol has been well documented [28]. At low doses, ethanol acts as a stimulant; at highh doses, it is a CNS depressant. Increases in locomotor

activity, referred to as "ethanol-induced excitation", have been reported in randomly-bred Swiss Webster and N.M.R.I. mice as well as in the rat [4, 17, 26]. The BALB strain may exhibit such an excitation at low and moderate doses of alcohol as well as increased sensitivity to CNS depression at anesthetic doses, while the C57BL strain may be relatively insensitive to both effects. Different and separate mechanisms of action may be responsible for ethanol-induced stimulation and depression, and these mechanisms may, in turn, show genetic variation among inbred mouse strains. The exact action of alcohol, as well as its target site in the CNS, still remains elusive, although selective depression of the reticular formation has been repeatedly suggested [8]. However, the reticular formation is a multisynaptic complex and the possibility of separate mechanisms controlling excitation and depression is thus not untenable.

Ethanol-induced increases in activity are suggested to be adrenergic in origin and related to alteration of norepinephrine and/or dopamine synthesis [4], while ethanol-induced depression, at least at anesthetic doses, is believed to have a cholinergic basis [5]. Strain differences in endogenous and/or ethanol-induced serotonin [9,15] and norepinephrine [25] levels have also been reported for the C57BL, BALB and DBA strains and these differences may be related to the differential behavioral findings observed with ethanol as well as with other comparably acting substances.

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