

Increased drinking during withdrawal from intermittent ethanol exposure is blocked by the CRF receptor antagonist D-Phe-CRF(12-41).

Abstract

BACKGROUND:

Studies in rodents have determined that intermittent exposure to alcohol vapor can increase subsequent ethanol self-administration, measured with operant and 2-bottle choice procedures. Two key procedural factors in demonstrating increased alcohol intake are the establishment of stable alcohol self-administration before alcohol vapor exposure and the number of bouts of intermittent vapor exposure. The present studies provide additional behavioral validation and initial pharmacological validation of this withdrawal-associated drinking procedure.

METHODS:

Studies at 2 different sites (Portland and Scripps) examined the effect of intermittent ethanol vapor exposure (3 cycles of 16 hours of ethanol vapor+8 hours air) on 2-hour limited access ethanol preference drinking in male C57BL/6 mice. Separate studies tested 10 or 15% (v/v) ethanol concentrations, and measured intake during the circadian dark. In one study, before measuring ethanol intake after the second bout of intermittent vapor exposure, mice were tested for handling-induced convulsions (HICs) indicative of physical dependence on ethanol. In a second study, the effect of bilateral infusions of the corticotropin-releasing factor (CRF) receptor antagonist D-Phe-CRF(12-41) (0.25 microg/0.5 microL) into the central nucleus of the amygdala (CeA) on ethanol intake was compared in vapor-exposed animals and air controls.

RESULTS:

Intermittent ethanol vapor exposure significantly increased ethanol intake by 30 to 40%, and the mice had higher blood ethanol concentrations than controls. Intra-amygdala infusions of D-Phe-CRF(12-41) significantly decreased the withdrawal-associated increase in ethanol intake without altering ethanol consumption in controls. Following the second bout of intermittent vapor exposure,

mice exhibited an increase in HICs, when compared with their own baseline scores or the air controls.

CONCLUSIONS:

Intermittent alcohol vapor exposure significantly increased alcohol intake and produced signs of physical dependence. Initial pharmacological studies suggest that manipulation of the CRF system in the CeA can block this increased alcohol intake.