INDIVIDUAL DIFFERENCES IN ADDICTION-LIKE BEHAVIORS AND SENSITIVITY TO ETHANOL IN DEPENDENT AND NONDEPENDENT HETEROGENEOUS STOCK RATS

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Over 175 million Americans use alcohol each year, and ~16% of those people develop Alcohol Use Disorder (AUD). This suggests there are significant individual differences related to the development of problematic drinking, which could be, in part, related to genetic differences. Heterogeneous stock rats are genetically and phenotypically diverse rats and have previously been used to investigate genetic differences related to compulsive-like drug-taking, thus may be useful for investigating individual differences in alcohol addiction-like behaviors and response to medications. In this study, male and female heterogeneous stock rats self-administered oral ethanol (10% v/v) on a fixed ratio 1 schedule of reinforcement until a stable baseline of intake was measured. Then, multiple addiction-related behaviors (i.e., preference for ethanol over water, progressive ratio responding, level of quinine-adulterated ethanol intake) were measured. Dependence was then induced using the chronic intermittent ethanol vapor exposure (14 hours/day x 4 weeks, achieving blood ethanol levels of 150-250 mg%) and behavioral experiments were conducted during acute withdrawal (6-8 hours after vapor) from ethanol. Escalation of ethanol intake (increase in level of intake under fixed ratio conditions), motivation to obtain ethanol (responding under progressive ratio), compulsivity (level of quinine-adulterated ethanol intake) as well as measurement of sensitivity to alcohol (loss of righting reflex), somatic withdrawal signs, and withdrawal-induced hyperalgesia (using the mechanical sensitivity test) were measured. We computed an Addiction Index from the mean Z scores from each of the five measurements. Female rats had higher levels of ethanol intake before and after induction of dependence and escalated more quickly than male rats. Females also showed higher motivation and compulsivity (as demonstrated by the higher breakpoint in the progressive ratio test and the lower sensitivity to quinine adulteration), compared to males. Although all rats showed withdrawal-induced increases in hyperalgesia, no sex differences were observed. However, females were significantly less sensitive to alcohol in the loss of righting reflex task. There were robust individual differences in the Addiction Index, suggesting heterogeneous stock rats exhibit diverse AUD-related phenotypes that are likely related to genetic factors influencing the development of AUD. These findings highlight the importance of pharmacogenetic studies, and suggest potential implementation of precision medicine when treating AUD.