

# Different molecular/behavioral endophenotypes in C57BL/6J mice predict the impact of OX1 receptor blockade on binge-like ethanol intake

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Ethanol (EtOH) research has focused on stages of dependence. It is of paramount importance to more deeply understand the neurobehavioral factors promoting increased risk for EtOH binge drinking during the early stages of the addiction cycle. The first objective of this study was to evaluate whether C57BL/6J mice showing high drinking in the dark (DID) exhibit neurobehavioral traits known to contribute to EtOH binge-drinking disorders. Comparing high vs. low drinkers (HD/LD), we evaluated different types of basal anxiety-like responses, EtOH preference and sensitivity to the reinforcing properties of EtOH, and basal mRNA expression of the OX1/OX2 receptors (OX1r/OX2r) within the prefrontal cortex (PFC) and the nucleus accumbens (NAcc). Additionally, we tested binge drinking by LD/HD in response to a selective OX1r antagonist following intermittent episodes of DID (iDID). We report that DID consistently segregates two neurobehavioral endophenotypes, HD vs. LD, showing differences in neophobia and/or impulsivity/compulsivity traits. Additionally, HD mice show decreased basal OX1r and OX2r mRNA expression within the NAcc and elevated OX1r within the PFC. Exposure to several intermittent episodes of EtOH DID triggered a rapid increase in EtOH intake over time in LD mice matching that observed in HD mice. Despite HD/LD endophenotypes did not show differences in EtOH intake, they still predicted the response to a pharmacological challenge with a selective OX1r antagonist. The present data underscore the relevance of HD/LD endophenotypes stemming from DID procedures for exploring neurobehavioral processes underlying the early stages of the addiction cycle and EtOH binge-drinking disorders. ©

Anxiety

Endophenotype

Impulsivity/compulsivity

Intermittent ethanol drinking in the dark

Neophobia

Orexin

1 (2 methyl 6 benzoxazolyl) 3 (1,5 naphthyridin 4 yl)urea

alcohol

messenger RNA

orexin 1 receptor

orexin 2 receptor

adult

alcohol consumption

animal experiment

animal tissue

anxiety

Article

binge drinking

C57BL 6 mouse

conditioned place preference test

controlled study

elevated plus maze test

endophenotype

enzyme inhibition

exploratory behavior test

gene expression

impulsiveness

male

mouse

neophobia

nonhuman

nucleus accumbens

prefrontal cortex

taste preference