Period2 gene deletion abolishes αMelanocyte stimulating hormone response to ethanol

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PERIOD2 GENE DELETION ABOLISHES αMELANOCYTE STIMULATING HORMONE RESPONSE TO ETHANOL

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INTRODUCTION

Proopiomelanocortin (POMC)-producing neurons in the arcuate nucleus of the hypothalamus secrete αMSH (1). Studies have shown that αMSH plays an important role in the regulation of several biological functions including a role in physiological responses to drug of abuse (2). There is accumulating evidence that the neurotropic αMSH modulates neurobiologic responses to ethanol. First, αMSH is expressed in brains regions implicated in ethanol’s effects (3, 4). Second, chronic exposure to ethanol significantly reduced, while abstinence following chronic ethanol exposure increased, endogenous αMSH immunoreactivity in specific brain regions of Sprague-Dawley rats (5, 6). Our lab has shown that in adults and fetal rats, alcohol exposure alters POMC gene expression and the β-endorphin peptide release from the hypothalamus (7). Since, both α-MSH and β-endorphin peptides are produced from POMC precursor gene, the possibility arose that the level of α-MSH in the hypothalamus is similarly altered by alcohol exposure. Thus, in this study we used the neonatal mouse model to determine whether acute or chronic alcohol exposures alter levels of α-MSH and POMC mRNA in the hypothalamus.

Recently, an interaction between αMSH and a clock gene Period 2 (Per2) has been demonstrated in the hypothalamus. Yang et al. (2009) demonstrated that Per2 suppresses feeding during the inactive period by regulating the circadian rhythm of αMSH expression in the hypothalamus (8). In addition, their lab provided evidence that alcohol feeding in females and adults alters circadian rhythms of Period genes (Per1, Per2, Per3) in the hypothalamus (7). Clinical studies revealed that alcoholics with a specific set of polymorphisms in the Per2 gene consume less alcohol than alcoholics without the polymorphisms (9). Hence, Per2 appears to be a targeted gene whose expression may be altered by alcohol which may act on all circadian functions. In order to elucidate the role of Per2 gene in modulation of neurobiologic responses to ethanol, we examined the effect of Per2 mutation on hypothalamic αMSH neuronal responses to acute and chronic ethanol.

MATERIALS AND METHODS

Animals Methods

To study the effect of both acute and chronic ethanol administration on αMSH level of hypothalamic neurons of control and Per2 knockout mice. The Pregnant C57BL/6 and Per2 mutant mice were individually housed in 12 hour light/12 hour dark cycles. The newborn mice (C57BL/6 and Per2 mutant mice) were treated with ethanol in the following way: the acute ethanol exposure animals were given treatment on day PD7, whereas the chronic ethanol exposure animals received treatment from PD2-PD7. At day of treatment two pups from each litter were fed by intubation with milk formula containing 11.34% (vol/vol) alcohol (alcohol fed - AF), a solution (0.1-.2 ml/animal; 2.5g/kg; or an isocaloric volume of maltose dextrin (pair fed - PF) as in Goodlet et al., (1998); or leave alone (ad libitum - AD). The feeding was conducted at 1000 and 1200 h daily. After feeding, the pups were immediately returned to the litter. One hour after the last feeding, brains were collected and the medial basal hypothalamic tissue was divided into halves. One half was used for gene expression analyses and the other used to measure αMSH levels in the hypothalamus. Six animals per treatment were used (a total of 18 animals were used per experiment). The samples were stored accordingly. Animal care and treatment were performed in accordance with institutional guidelines, and approved by the Rutgers Animal Care and Facilities Committee and conformed with the NIH Guide for the care and use of laboratory animals (NIH publication 85-23, revised 1996).

RESULTS

In light of the above observations, the data support the involvement of Per2 gene in mediating the POMC neurons response to ethanol.

COMPARING THE RESPONSE OF PROPOMELANOCORTIN (POMC) mRNA LEVELS IN C57BL/6 AND PER2 MUTANT MICE UPON ACUTE AND CHRONIC ETHANOL (ETOH) EXPOSURES

REFERENCE