Title

SEX AND GENOTYPE DEPENDENT DRUG-INDUCED DOPAMINE RELEASE IN ADOLESCENT CHRNA6 3'-UTR RATS

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SEX AND GENOTYPE DEPENDENT DRUG-INDUCED DOPAMINE RELEASE IN ADOLESCENT CHRNA6 3'-UTR RATS

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Introduction: The rewarding effects of drugs of abuse are associated with the dopaminergic system in the limbic circuitry. Nicotine exposure during adolescence is linked to increased use of drugs of abuse, and nicotine and methamphetamine (Meth) are commonly used together. Nicotine modulates neuronal nicotinic acetylcholine receptor (nAChR) systems which are critical for reward processing and drug reinforcement, whereas Meth evokes greater efflux of dopamine (DA) in the reward system. A single nucleotide polymorphism (SNP) in the 3'-untranslated region (UTR) of the α6 nicotinic receptor subunit gene CHRNA6, rs2304297, was associated with tobacco/nicotine and general substance use during adolescence. Using CRISPR-Cas9 genomic engineering our lab recapitulated the CHRNA6 3'UTRC123G SNP, generating 훼6CC and 훼6GG allele carriers. We hypothesized the CHRNA6 3'UTRC123G SNP would sex- and genotype-dependently enhance drug-induced DA release in the nucleus accumbens shell of adolescent 훼6GG and 훼6CC carriers.

Methods: Adolescent male and female, underwent a 4-day sub-chronic, low-dose (0.03 mg/kg/0.1 mL x 2) nicotine pretreatment paradigm to assess nicotine- and Meth (0.02 mg/kg/0.1 mL x 2)-induced DA release in the nucleus accumbens shell using in vivo microdialysis coupled with high-performance liquid-chromatography-electrochemical detection (HPLC-ECD).

Results: Nicotine and Meth-induced DA release is enhanced in 훼6CC females, primarily in the acute condition as compared to 훼6G females. Nicotine and Meth induced DA release is enhanced in 훼6GG males independent of pretreatment, but no genotype differences were observed.

Conclusion: These findings provide evidence that the CHRNA6 3'-UTR SNP is functional in DAergic neurons and regulates the release of DA in males and females differently.

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THE EFFECT OF ALCOHOL ON MITOCHONDRIAL ALTERATIONS IN THE FRONTAL LOBE INDUCED BY RMTBI IN ADOLESCENCE

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Adolescents participating in sports are more likely than non-athletic peers to incur traumatic brain injuries (TBI) and frequently participate in at risk alcohol consumption. Injury resolution requires intact cellular bioenergetics to produce ATP to sustain enerqy requirement post-injury processes. Unfortunately, damaged mitochondria, which are responsible for generating most of the cellular ATP, may be affected following TBI. Moreover, alcohol consumption can hinder mitochondrial function, specifically fusion and fission process, resulting in further damage. The mechanisms leading to increased damage, are not well understood. This exploratory study aimed to elucidate how the impact of repeated-mild TBI (rmTBI) and alcohol exposure may influence mitochondrial fusion and fission activity in the frontal lobe in adolescent male rats. Adolescent male Wistar rats were randomly assigned to one of four groups: i) Sham + Air (control), ii) Sham + EtOH, iii) rmTBI + Air, or iv) rmTBI + EtOH. Beginning on postnatal day 45, animals received 3-days of intermittent alcohol vapor (14 h on/10 h off), one day of respite, then either a mTBI produced by weight drop, or a sham procedure. This pattern was repeated for four cycles, followed by a 7-day respite before euthanasia and excision of brains. Frontal lobe samples were extracted for Western blot analysis. Results revealed elevated mitochondrial expression of OPA1, a mitochondrial fusion protein in the rmTBI + EtOH group. These preliminary findings suggest increased mitochondrial fusion activity. Additionally, COX-IV to GAPDH ratio was significantly higher in frontal lobe of Sham + EtOH group than in that of sham/air controls. These differences imply a potential link between increased mitochondrial respiratory capacity or quantity and alcohol consumption. These findings suggest altered integrity of mitochondrial homeostasis as a possible mechanism underlying sequela from rmTBI and alcohol exposure. This research was supported by NIH/NIAAA R01 AA025792 (PEM, NWG) & T32 AA007577 (PEM).

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DIET-INDUCED OBESITY INDUCES TRANSCRIPTOMIC CHANGES IN NEUROIMMUNOMETABOLIC-RELATED GENES IN THE STRIATUM AND OLFACTORY BULB.

Colina-Prisco C [1,2], Jaime-Lara RB [1,2,3], De Jesus Vega M [1], Matikainen-Ankney B [4], Brooks B [2], Wang Y [2], Franks A [2], Kravitz A [4], Joseph PV [1,2]

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The incidence of obesity has markedly increased globally over the last several decades, which is believed to be associated with an easier availability of energy-dense foods, including high-fat foods. The reinforcing hedonic properties of high-fat foods, including olfactory cues, activate reward centers in the brain, motivating eating behavior. Thus, there is a growing interest in the understanding of the genetic changes that occur in the brain associated with obesity and eating behavior. This growing interest has paralleled advances in genomic methods that enable transcriptomic-wide analyses. Here, we examined the transcriptomic-level differences in the olfactory bulb and striatum, regions of the brain associated with olfaction and hedonic food-seeking, respectively, in high-fat diet (HFD)-fed obese mice using HiSeq 2500 system. To isolate the dietary effects from obesity, we also examined transcriptomic changes in normal chow- and limited HFD-fed groups, with the latter being pair-fed with a HFD isocaloric to the consumption of the normal chow-fed mice. Using RNA sequencing, we identified 274 differentially expressed genes (DEGs) in the striatum and 11 in the olfactory bulb of ad libitum HFD-fed mice compared to the chow-fed group, and thirty-eight DEGs in the striatum between the ad libitum HFD- and limited-HFD-fed groups. The DEGs in both tissues were associated with inflammation and immune-related pathways, including oxidative stress and immune function, and with mitochondrial dysfunction and reward pathways in the striatum. These results shed light on potential obesity-associated genes in these regions of the mouse brain.

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