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Enhanced nicotine reward in a mouse model of the P129T FAAH gene polymorphism

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A single nucleotide polymorphism of the human fatty acid amide hydrolase (FAAH) gene leads to a missense mutation (C385A) that substitutes a proline residue for threonine (P129T). Clinical studies report an association between the P129T mutation, reward-related pathologies and problem drug use. The current study employed a P129T knock-in (KI) mouse model to characterize the effects of this SNP on the rewarding effects of nicotine using conditioned place-preference (CPP), operant intravenous self-administration (IVSA) and in vivo microdialysis procedures. The results revealed genotypic differences such that P129T KI mice exhibit enhanced sensitivity to low doses of nicotine reward relative to WT in the CPP paradigm. P129T KI mice also acquire nicotine IVSA more quickly, display an upward shift in the dose response, and achieve higher breakpoints during the progressive ratio test. Operant behavior was rapidly extinguished in WT mice upon saline substitution. Finally, P129T mice exhibit enhanced nicotine-induced elevations in NAc DA levels than their WT counterparts. Preliminary findings using a chemo-proteomics approach reveal region-specific changes in FAAH activity in areas associated with nicotine reinforcement, such as the dorsal striatum. Collectively, these data suggest that nicotine reward is enhanced in mice expressing the P129T mutation. The mechanisms by which genetic disruption of FAAH enhance sensitivity to nicotine likely involve dopamine transmission in terminal regions of the mesolimbic pathway. This work was supported by NIH funding including P01 DA017259, K99 AA025393, and R00 DA035865.