Phenotypic and Serotonergic Targets for Therapeutics in Addictive Disorders

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Cocaine abuse and addiction continue to extract considerable personal, health and societal tolls across the globe. The cycling progressive nature of this disorder stymies efforts to stay abstinent with relapse oft precipitated by impulsive action (predisposition toward rapid, unplanned reactions to stimuli without regard to negative consequences) and craving in the face of exposure to cocaine-associated cues (cocaine cue reactivity). Dr. Cunningham will discuss her translational research to suggest that convergence of the impulsivity trait with the dynamic state of cue reactivity is a synergy that contributes to greater vulnerability to relapse in animal and human studies. Furthermore, impulsivity and cue reactivity are mechanistically-linked to disrupted serotonin (5-HT) signaling through the 5-HT2A receptor (5-HT2AR) and 5-HT2CR localized to the medial prefrontal cortex (mPFC). In preclinical models, native 5-HT2AR and 5-HT2CR protein expression in the mPFC predicts the intensity of impulsivity and cue reactivity while an engineered knockdown of the 5-HT2CR in the mPFC results in an aggregate maladaptive behavioral phenotype, a compensatory upregulation of the 5-HT2AR protein expression, and enhanced pharmacological sensitivity to a 5-HT2AR antagonist. These data suggest that there is an interactive relationship between the 5-HT2AR and 5-HT2CR in the mPFC, and that a 5-HT2AR:5-HT2CR imbalance may be a functionally-relevant mechanism underlying addiction phenotypes. She will conclude with a discussion of novel chemical entities geared to restore the 5-HT2AR:5-HT2CR balance to repair cortical deficits and ameliorate relapse during abstinence from cocaine addiction.