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Cocaine Intravenous Self-Administration In Near-Isogenic Spontaneously Hypertensive Rat Substrains Bred In-House and QTL Analysis of Cocaine Locomotor Sensitivity and Gene Expression (RNA, Protein) in an F2 Cross

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Psychostimulant use disorders have ~40-50% heritability, yet few loci have been identified as risk factors or targets for treatment. Quantitative trait locus (QTL) mapping in near-isogenic rodent substrains showing trait variation facilitates identification of quantitative trait genes/variants underlying gene expression and behavior. We previously found enhanced cocaine locomotor sensitivity, impulsivity and compulsivity in SHR/NCrl vs. SHR/NHsd substrains purchased from their respective vendors (Charles River Laboratories, Harlan-Innotiv Laboratories) and following in-house breeding. After establishing a colony, adult rats were tested for the rate of spontaneous acquisition (no previous pellet training) of cocaine (0.3mg/kg) self-administration. To test for motivation to acquire cocaine, requirements progressed through FR1-FR5 and a progressive ratio schedule with exponentially increasing required lever presses for one infusion of cocaine. Different cocaine doses (1.0, 0.1, and 0.01mg/kg) are being substituted to establish a dose-response curve and finally, rats complete extinction training and are assessed for cue-induced reinstatement. SHR/NCrl rats exhibited higher active lever responding during FR1-FR5 than SHR/NHsd, replicating the substrain pro-addiction phenotype. We are currently running behavioral QTL analysis of cocaine locomotion and sucrose preference, as well as eQTL and protein QTL analysis of striatum and frontal cortex on a subset of rats from a reciprocal F2 cross of the SHR substrains with the goal of triangulating on candidate genes/variants influencing all three trait types.