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Spontaneously Hypertensive Rat substrains and the offspring of reciprocal F2 crosses exhibit differences in addiction risk traits and cocaine behavioral sensitivity

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Psychostimulant use disorders have ~40-50% heritability. Quantitative trait locus (QTL) mapping in nearly identical rodent substrains facilitates identification of quantitative trait genes/variants underlying behavior. We previously found enhanced cocaine locomotor sensitivity and self-administration in SHR/NCrl vs. SHR/NHsd substrains purchased from their respective vendors (Charles River Laboratories, Harlan Envigio Laboratories). Following in-house breeding of parental substrains and F2 crosses, adult rats were assessed for locomotor activity following saline, and cocaine (5, 20mg/kg; i.p), and on a sucrose preference task. Additionally, rats from parental substrains were tested on a Differential Reinforcement of Low-Rate Responding (DRL) operant task which required response inhibition to assess impulsivity and intravenous operant cocaine (0.25 mg/kg) self-administration sessions under an FR1 reinforcement schedule. SHR/NCrl rats exhibited greater locomotor activity when first injected with saline (novelty response) and greater conditioned hyperactivity compared to SHR/NHsd following repeated injections of cocaine. Regardless of substrain, females displayed a greater novelty response and cocaine-induced locomotion than males. SHR/NHsd showed a stronger sucrose preference, indicating reward-type sensitivity. Consistent with a more addiction-prone phenotype, on the DRL task, SHR/NCrl rats exhibited lower response efficiency and sex-dependent increases in burst responding, indicative of impulsivity. Females from both substrains self-administered more cocaine than males. Reciprocal F2 offspring (one-half had SHR/NCrl grandsire, one-half had SHR/NHsd grandsire) revealed higher cocaine-induced locomotion and sensitization in females regardless of paternal lineage of origin, however, the F2s with SHR/NHsd grandsires exhibited higher sucrose preference scores than those with SHR/NCrl grandsires, indicating a parent of origin effect. These results demonstrate heritable differences in pro-addiction phenotypes amongst near-isogenic substrains and their reciprocal F2 offspring.