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Premorbid addiction model traits and cocaine stimulant sensitivity in spontaneously hypertensive rat (SHR) substrains

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Psychostimulant use disorders are heritable (40-50%) with a largely unknown genetic etiology. Forward genetic mapping in closely related rodent substrains, termed reduced complexity crosses (RCC) can rapidly identify quantitative trait genes/variants underlying behavior, capitalizing on their near-isogenic nature. We previously observed differences in addiction model traits, including cocaine stimulant sensitivity and operant intravenous self-administration between spontaneously hypertensive rat substrain (SHR) from either Harlan-Envigo Laboratories (SHR/NHsd) or Charles River Laboratories (SHR/NCrl). Following in-house breeding to remove environmental variance, female and male adult rats were assessed for locomotor activity following saline, and two doses of cocaine (5 and 20mg/kg, i.p.) over two weeks. Rats were also tested on a sucrose preference task for a natural reward and a novelty preference task. Rats then underwent a Differential Reinforcement of Low-Rate Responding (DRL) operant task requiring inhibited responding to earn sucrose pellets and schedule-induced polydipsia (SIP), that assesses habitual and excessive water drinking (models for impulsivity and compulsivity). SHR/NCrl exhibited greater locomotor activity when first injected with saline (novelty response) and SHR/NCrl showed greater conditioned hyperactivity in response to saline following repeated (3) injections of cocaine (20mg/kg, i.p.). Further, within SHR/NCrl, females exhibited a greater novelty response and greater cocaine-induced locomotion than males with both doses of cocaine, and a greater conditioned effect on saline days following both doses. Alternatively, SHR/NHsd drank more sucrose than SHR/NCrl in the sucrose preference test suggesting substrain differences depending on the type of reward, with female SHR/NHsd drinking more sucrose by body weight than males.