Short-term selective breeding for adolescent sensitivity to tetrahydrocannabinol-(THC-) induced locomotor sedation in mice.

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Adolescent cannabis use is a growing problem in the US despite the considerable role that endocannabinoid systems play in normal brain development (Volkow et al., 2014). The goals of the current project are to determine the extent to which genotype influences adolescent locomotor sensitivity to the sedative effects of tetrahydrocannabinol (THC; psychoactive component of cannabis), and whether genes that influence such sensitivity also influence other adolescent (and adult) phenotypes. Using a short-term selective breeding strategy originating from a B6D2F2 founding population (created by crossing C57BL/6J dams with DBA/2J sires), we have initiated the production of mouse lines exhibiting high and low adolescent sensitivity to THC in a 20 min locomotor activity test. Adolescent (postnatal day 28-32) F2 males and females were assessed for locomotor sensitivity to a 10mg/kg THC dose, and mice exhibiting high and low responses were chosen for subsequent breeding of selection generation 1 (S1). S1 offspring were then phenotyped and parents selected for the breeding of S2, and so on. We have selected mice through S3, and are currently setting up the parental breeders for S4. The mean THC-induced locomotor sedative responses (compared to baseline locomotion) for S3 offspring are -2,049.5 cm traveled for the high line, and -676.1 cm traveled for the low line. Response to selection through S3 appears stronger in the direction of high adolescent sensitivity to THC's locomotor sedative effects, with realized heritability (h^2) calculated at .46 and .27 for the high and low lines, respectively. Ongoing efforts are aimed at continuing selection through S4, as well as determining whether genes influencing high adolescent sensitivity to THC-induced locomotor sedation also influence other THC-related traits. For example, the testing of S2 offspring indicated that genetic selection for high and low adolescent sensitivity to THC-induced sedation produced mice that also differed in sedative response to THC in adulthood.

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