Repeated heroin induces locomotion, sensitisation and conditioned place preference in C57BL/6J mice but not in DBA/2J; association with alterations in MOP-r activation and dopamine transporter binding

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There is growing agreement that genetic factors play an important role in the risk to develop heroin addiction (Kreek et al., 2005). Two inbred strains of mice known to differ in their opiate-induced behaviours (Murphy et al., 2001) were examined for locomotor, conditioned place preference and sensitisation effect of heroin in these mice in an unbiased and paired CPP protocol. Heroin (4 mg/kg) induced locomotion, (P<0.001 vs saline), conditioned place preference (P<0.001 vs saline) and sensitisation (P=0.001 on the 4th day of conditioning vs day 1 of conditioning) in male C57BL/6J (20-25 g) mice but not in male DBA/2J (20-25 gr) (P>0.05 vs saline controls) (three way ANOVA with LSD post hoc test, n=15). In order to investigate the neurobiological substrate underlying these differences, the effect of chronic “intermittent” heroin administration on the opioid and dopaminergic system was explored. Both strains were injected with saline or heroin in a chronic “intermittent” escalating dose paradigm (heroin: 2x1 mg/kg/injection on day 1, 2x2 mg/kg/injection on days 2 and 3, 2x4 mg/kg/injection on days 4 and 5, and 2x8 mg/kg/injection on days 6 and 7). The two subcutaneous injections were given daily at 9 a.m and 5 p.m. Twice as much µ-opioid receptor (MOP-r) stimulated [35S]GTPγS binding was observed in the nucleus accumbens of C57BL/6J mice vs DBA/2J (10.2 ±1.8 KBq/mg vs 4.6±1.6 KBq/mg, P<0.05 in nucleus accumbens core of saline treated mice; 8.6±1.8 KBq/mg vs 3.7±1.4 KBq/mg, P<0.05 in nucleus accumbens shell of saline treated mice; 10.5±1.8 KBq/mg vs 4.3±1.9 KBq/mg, P<0.01 in nucleus accumbens core of heroin treated mice; 8.6±1.5 KBq/mg vs 3.6±1.6 KBq/mg, P<0.05 in nucleus accumbens shell of heroin treated mice) (three way ANOVA with LSD post hoc test, n=7). Heroin decreased MOP-r density in the nucleus accumbens shell (90.3±4.0 fmol/mg vs 71.9±2.3 fmol/mg; P<0.05) and central medial thalamus (131.0±9.4 fmol/mg vs 113.7±3.9 fmol/mg; P<0.05) of C57BL/6J mice, but not in DBA/2J (P>0.05) (three way ANOVA with LSD post hoc test, n=6). Higher levels of dopamine transporters were observed in the nucleus accumbens shell (258.1±17.7 fmol/mg vs 197.6±25.6 fmol/mg; P<0.05), tubercle (251.9±22.3 fmol/mg vs 148.7±16.6 fmol/mg; P<0.001) and caudate putamen (270.9±12.8 fmol/mg vs 211.3±14.8 fmol/mg; P<0.05) of heroin treated DBA/2J mice compared to heroin treated C57BL/6J (three way ANOVA with LSD post hoc test, n=6). No strain or treatment effects were observed in KOP-r, D1 and D2 binding (P>0.05, n=6). These strain differences in MOP-r activity and differences in the regulation of the dopamine transporter may be responsible for the heroin induced differences in behavioural phenotype.
