The effects of prenatal stress on cocaine reward, cocaine locomotion and sensorimotor processing are heritable in the BXD recombinant inbred strain panel

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Early life stress has been implicated in a number of psychiatric conditions, including addiction and schizophrenia, and appears to be involved in complex gene X environment interaction leading to pathology. To dissect this interaction, we have been examining the impact of prenatal stress (PNS) on cocaine-seeking and sensorimotor processing in mice with different genetic backgrounds. Previously, we found that PNS in C57BL/6 (B6) but not and DBA/2 (D2) increased the magnitude of cocaine-induced conditioned place preference (CPP) and cocaine induced locomotion whereas PNS in D2, but not B6, impaired pre-pulse inhibition (PPI) of acoustic startle. Identification of the alleles mediating these interactions is an important step in understanding the underlying neurobiology. In order to work towards this goal, we have characterized the effects of PNS on BXD recombinant inbred strains. These strains each possess unique combinations of B6 and D2 alleles and will allow for identification of quantitative trait loci (QTLs) that mediate the effects of PNS. **Methods.** BXD strains were subject to timed mating followed by assignment to PNS and control groups. PNS dams were placed in a restraint stress protocol (1 hour restraint, 3 times daily) starting on embryonic day (E) 11 to 14 and continued until parturition. PNS may affect developmental outcomes by altering maternal behavior in the post-natal period. Accordingly, the frequency of pup-dam contact was measured in the first 10 post-natal days. Adult control and PNS offspring (8 to 9 weeks) were tested in a PPI procedure (110 dB startle, 74 and 90 dB PPI) followed by cocaine CPP (10 mg/kg cocaine I.P.). **Results.** We have found PNS by strain interactions, indicating the effects of PNS are heritable in the BXD panel. Specifically, PNS interacts with strain to alter cocaine acute locomotion, locomotion sensitization and CPP, acoustic startle response and PPI. PNS interacts with strain to alter pup-dam contact, with the most frequent effect being a reduction in contact. Interestingly, the PNS strain effect on maternal behavior correlates with the PNS strain effects on cocaine reward/locomotion, but not with startle or PPI, indicating the effects of PNS on cocaine related behaviors may be mediated by changes to maternal behavior in the post-natal period. Overall, these results suggest that the effects of PNS on cocaine reward/locomotion, sensorimotor gating and maternal stress responsivity are heritable in the BXD panel. Future work will seek to identify QTLs, and ultimately polymorphisms, that mediate the effects of PNS. This research may serve to elucidate the gene by environment interactions that lead to the development of psychiatric disorders.