MODELLING THE INDIVIDUAL VARIABILITY TO DEVELOP HEROIN DEPENDENCE IN OUTBRED NIH HETEROGENEOUS STOCK RATS

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Introduction: Drug addiction is a chronic relapsing disorder characterized by compulsive drug seeking and use despite harmful consequences.Recently, in the USA the abuse of prescription opioid analgesics caused a recrudescence of heroin dependence epidemic, as patients switch to heroin once the prescribed opioid is withhold. Drug-dependence develops only in a subset of vulnerable subjects, whereas the majority of drug users maintains control over drug-use.Understanding the biological bases of opioid addiction vulnerability would provide a valuable help for the development of personalized treatment strategies for pain therapy and for heroin dependent individuals. For this purpose we used outbred NIH Heterogeneous Stock (HS) rats, a line characterized by a large genetic variability similar to the human population, to develop a behavioral preclinical model of individual variability in heroin dependence vulnerability.

Materials and methods: Male and female HS rats were trained to a 1h short-access (ShA) heroin (60μg/kg/infusion) self-administration(SA) sessions for 10 days and then they were switched to 12h long-access (LgA) sessions for additional 8 days. At the end of LgA training, three criteria for heroin dependence were scored: escalation of heroin intake, measured as the difference in infusions earned in the 1st hour of the last 2LgA sessions minus the infusions earned in the last 2ShA sessions; motivation for heroin measured as the break point reached in the progressive ratio schedule of reinforcement session and relapse induced by a priming dose of heroin. To verify that the pattern of individual vulnerability to heroin in outbred NIH-HS is different from genetically more homogeneous, inbred lines, we compared heroin taking and seeking to that of two (Wistar Kyoto (W/K) and Fisher 344 (F344)) of the eight inbred rat lines used to generate the HS.In addition, we performed Neuroimaging before and after heroin exposure to investigate if and how the drug can modify brain structure. Finally, we performed a Regression Tree analysis to verify if and to what extend data about heroin motivation and escalation could be predictive of the relapse to heroin use.

Results: F344 rats showed a higher break point compared to W/Kand NIH-HS, whereas W/K showed lower priming reinstatement respect to the other two lines. We then pooled NIH-HS, W/K and F344 in a single population, and for each of the three addiction criteria we transformed individual values in z-scores. Z-scores were then averaged to calculate the individual global addiction score (GAS). Analysis of GAS revealed that both F344 and W/K are different from NIH-HS with F344 being in the upper extreme of the distribution and W/K in the lower, while NIH-HS are clustered in the middle with few subjects spreading toward both extremes. Neuroimaging results showed that there was a reduction of the brain grey matter after heroin exposure, which is in line with human data. Regression tree analysis demonstrated that motivation and escalation of heroin intake can be used as relapse predictor.

Conclusion: Our data demonstrate that F344 and W/K represent respectively upper and lower propensity to develop opioid dependence and the genetically outbred HS rats include features of both lines, with few subjects showing propensity to develop opioid dependence andother showing resilience. The HS show heroin-induced neuroimaging biomarkers similar to humans patients and relapse ratio can be predicted by heroin history. Altogether, data indicate that the HS line is a suitable model to study the biological bases of individual variability for opioid dependence risk.