

Striatum transcriptome profile shift in repeated aggression mouse model quickly recovered to normal except for 12 circadian clock genes after fighting deprivation

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Key words: addiction; behavior; cAMP cascade; chronic social conflict; dopamine; dorsal striatum; endogenous opioids; nucleus accumbens; transcriptome

Both aggressive and aggression-deprived (AD) species represent pathologic cases intensely addressed in psychiatry and substance abuse disciplines. Previously, we reported that AD mice displayed a higher aggressive behavior score than the aggressive group, implying the manifestation of a withdrawal effect. We employed an animal model of chronic social conflicts, curated in our lab for more than 30 years. In the study, we pursued the task of evaluating key events in the dorsal striatum transcriptome of aggression experienced mice and AD species compared to controls using RNA-Seq profiling. Aggressive species were subjected to repeated social conflict encounters (fights) with regular positive (winners) experience in the course of 20 consecutive days (A20 group). This led to a profoundly shifted transcriptome expression profile relative to the control group, outlined by more than 1000 differentially expressed genes (DEGs). RNA-Seq cluster analysis revealed that elevated cyclic AMP (cAMP) signaling cascade and associated genes comprising 170 differentially expressed genes (DEGs) in aggressive (A20) species were accompanied by a downturn in the majority of other metabolic/signaling gene networks (839 DEGs) via the activation of transcriptional repressor DEGs. Fourteen days of a consecutive fighting deprivation period (AD group) featured the basic restoration of the normal (control) transcriptome expression profile yielding only 62 DEGs against the control. Notably, we observed a network of 12 coordinated DEG Transcription Factor (TF) activators from 62 DEGs in total that were distinctly altered in AD compared to control group, underlining the distinct transcription programs featuring AD group, partly retained from the aggressive encounters and not restored to normal in 14 days. We found circadian clock TFs among them, reported previously as a withdrawal effect factor. We conclude that the aggressive phenotype selection with positive reward effect (winning) manifests an addiction model featuring a distinct opioid-related withdrawal effect in AD group. Along with reporting profound transcriptome alteration in A20 group and gaining some insight on its specifics, we outline specific TF activator gene networks associated with transcriptional repression in affected species compared to controls, outlining *Nr1d1* as a primary candidate, thus offering putative therapeutic targets in opioid-induced withdrawal treatment.