ALPRAZOLAM EXPOSURE DURING ADOLESCENCE DYSREGULATES SECOND MESSENGER SIGNALING IN THE MESOLIMBIC DOPAMINE REWARD SYSTEM

Benzodiazepines (BDZs) are widely prescribed due to their efficacy as anxiolytics, muscle relaxants, hypnotics and anticonvulsants. However, they possess adverse effects such as abuse liability and dependence. Alprazolam (Xanax) is one of the most commonly prescribed psychotropic medications in the US, accounting for ~48 million prescriptions dispensed in 2013. Despite its potential for misuse and addiction, increasing prescription rates have persisted. Even more concerning is that BDZs are commonly co-abused with opioids: ~33% of opioid overdoses deaths occurred with BDZs co-ingestion. An increased abuse of BDZs has been reported during adolescence, yet most of the available evidence about the neurobiological consequences and mechanism(s) underlying its abuse liability have been done in adult models. The present study was designed to investigate whether alprazolam (ALP) exposure during adolescence dysregulates the MAPK-signaling pathway, which has been shown to be regulated by drugs of abuse, and ultimately driving morphological and behavioral changes. Adolescent C5BL/6J male mice (PD 35) received an acute injection of ALP (1.0 mg/kg) or saline (SAL). Gene expression changes within the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC) and hippocampus (HIPP) were assessed 90 min after ALP injection using RT-qPCR. We measured whether the extracellular signal-regulated kinase 1/2 (ERK1/2) would be affected by ALP, given ERK’s role in regulating behavioral adaptations in reponse to drugs of abuse. Our results show a decrease in ERK2 gene expression within the VTA when compared to controls. Conversely, ERK2 gene expression was increased in the NAc, PFC and HIPP. Ongoing studies are currently assessing ERK 1/2 protein expression and its downstream targets (i.e., CREB, ELK-1 and cFos). Overall, these findings suggest that acute exposure to ALP during adolescence dysregulates ERK-signaling within brain regions implicated in both drug-reward and mood-related disorders.