Glutamate receptor dysregulation during protracted withdrawal from intermittent ethanol vapor in rats

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Functional dysregulation of glutamatergic receptor systems during withdrawal from chronic drug exposure is a primary driver of drug craving and subsequent resumption of drug use. Animal models (psychostimulants) have demonstrated dynamic alterations in both AMPA and NMDA receptor function and expression that contribute to drug seeking behavior. Regulation of these receptor systems can begin as early as a few days following cessation of drug use and are persistently expressed into long term withdrawal (>60d). Short term withdrawal from chronic ethanol exposure induces functional dysregulation of AMPA and NMDA receptors suggesting that similar mechanisms may be regulated across drugs. To this end, we investigated AMPA and NMDA receptor mediated synaptic function during protracted withdrawal (>35d) from chronic intermittent ethanol (CIE) exposure using whole cell patch clamp electrophysiology. We focused on the basolateral amygdala (BLA), as glutamatergic signaling in this region is robustly modulated by short term (24 h) withdrawal from CIE (and regulates anxiety like behavior expressed during withdrawal. Adolescent rats exposed to repeated cycles of CIE (12 hr/day, 4 d on/3 d off, 3 cycles) demonstrated significantly increased functional contributions of NMDA receptors in male but not female animals. TK30, a GluN3 antagonist and ifenprodil, a GluN2B antagonist significantly reduced responses in withdrawal but not control cells. In addition, we have measured an increased sensitivity to the GluA1 antagonist NASPM, suggesting an increased functional contribution of GluA1-containing AMPARs during protracted withdrawal. Our data support widespread dysregulation of glutamate signaling during protracted withdrawal from ethanol exposure.