The role of the rostromedial tegmental nucleus in withdrawal-induced negative affect

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Alcohol withdrawal is associated with a hypodopaminergic state and increased negative affect, both of which are thought to play a significant role in the propensity for relapse. The rostromedial tegmental nucleus (RMTg) exerts inhibitory control over midbrain dopamine neurons and activity within this region is associated with the aversive properties of cocaine and alcohol. Together these data suggest that the RMTg plays a role in mediating drug-induced aversive states. To investigate the role of the RMTg in withdrawal and withdrawal-induced negative affect, adult male Long-Evans rats were rendered ethanol dependent using chronic intermittent exposure to ethanol vapor and cFos expression, as well as measures of anxiety-like behavior and anhedonia, were evaluated across the time course of acute withdrawal (0, 6, 12, 24 hr after final ethanol exposure). cFos expression was significantly enhanced in the RMTg during acute withdrawal with peak expression occurring at the 12 hr time point when withdrawal symptom severity is also at its peak ($p \leq 0.01$). A similar pattern of cFos expression was observed in the lateral habenula – a region that sends prominent glutamatergic projections to the RMTg ($p \leq 0.01$). Likewise, ethanol dependent rats trained to self-administer intra-cranial electrical stimulation exhibited a significant rightward shift in responding across the time course of acute withdrawal with the greatest shift occurring 12 hrs after their final ethanol exposure compared to ethanol-naïve rats ($p \leq 0.05$). This resulted in a significant increase in reward threshold during withdrawal ($p \leq 0.05$). Finally, inhibition of the RMTg significantly attenuated withdrawal-induced increases in latency to enter the center of an open field ($p \leq 0.01$). Together these data suggest that the RMTg plays an important role in withdrawal-induced negative affect and therefore may be critically involved in the neurobiological mechanisms underlying relapse.

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