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MicroRNA-494 and CREB pathway: A role in the anxiolytic-like effects of acute ethanol

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Regulation of gene expression by microRNAs (miRNA) is an important epigenetic mechanism that could mediate chromatin remodeling leading to modulation of synaptic plasticity. The involvement of miRNA-494 as a possible chromatin remodeler was investigated via its actions on gene targets that in-turn could affect synaptic plasticity in the amygdala leading to the anxiolytic effects observed after acute ethanol exposure. Adult male Sprague-Dawley rats were intraperitoneally injected with ethanol (1g/kg) or n-saline and one hour after the injection, rats were subjected to anxiety-like behavioral measurements and amygdala tissue was immediately collected. Acute ethanol exposure resulted in a significant down-regulation of mature miRNA-494 mRNA within the amygdala. In order to further examine the downstream effects of miR-494, miR-494 function was next inhibited through the infusion of a locked nucleic acid (LNA™) modified antagomir directly into the central nucleus of amygdala (CeA). Rats received four bilateral CeA infusions of either aCSF, scrambled antagomir (500 pmol) or miRNA-494 antagomir (500 pmol) in the morning and evening for two consecutive days. On the third day, behavioral tests were performed and brains were immediately removed for biochemical analysis. Inhibition of miRNA-494 in the CeA was able to mimic the behavioral effects of ethanol by producing an anxiolytic response. No change was observed following infusion of the scrambled antagomir. One of the predicted target genes of miR-494 is Cited2 (*CBP/p300*- interacting transactivator 2) a novel candidate gene that regulates CREB signaling. mRNA expression of Cited2 and Cited2-related signaling genes such as *CBP* (*cAMP* response element binding protein) and *p300* was therefore measured. Protein levels of *CBP* and *p300* were also measured. The mRNA levels of *CBP*, *p300* and *Cited2* were up-regulated in both the ethanol and antagomir groups. Protein levels of CBP and p300 corroborated these results. Increases in levels of histone acetyltransferases (*CBP* and *p300*) following CeA antagomir infusion indicates a role of miR-494 signaling in chromatin remodeling. These results suggest a novel CREB pathway regulator in the amygdala which is possibly involved in anxiolytic effects of ethanol.

Biography

Tara Teppen is a Senior Research Scientist in the Department of Psychiatry at the University of Illinois at Chicago and Jesse Brown VA Medical Center, where she is currently studying the molecular mechanisms of acute and chronic alcohol use and withdrawal. She received her PhD in Neuroscience from Rosalind Franklin University and conducted two Postdoctoral trainings in the Department of Psychiatry at the University of Illinois at Chicago and in Research and Development at Jesse Brown VA Medical Center.

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