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Overexpression of Corticotrophin-Releasing Factor in the Nucleus Accumbens Enhances Nicotine-Induced Dopamine Release In Female, But Not Male Rats

Background: Prior work suggests that stress systems in the nucleus accumbens (NAc) promote the behavioral effects of nicotine in females. This hypothesis was based on our finding that overexpression of the stress peptide, corticotrophin-releasing factor (CRF), in the NAc selectively enhanced nicotine self-administration in female versus male rats. Additionally, overexpression of CRF in the NAc produced a greater upregulation of CRFR1 gene expression in female versus male rats. The present study assessed whether NAc CRF overexpression enhances nicotine-induced dopamine release in the NAc of females versus males. We also assessed nicotine-induced changes in the inhibitory neurotransmitter, γ -aminobutyric acid (GABA), given that CRFR1 receptors on GABA interneurons modulate dopamine release.

Methods: Adult female and male rats received intra-NAc infusions of an adeno-associated viral vector to overexpress CRF (AAV2/5-CRF) in one hemisphere and a control vector (AAV2/5-GFP) in the contralateral NAc. Three weeks later, the animals were prepared with dual microdialysis probes aimed into the NAc of both hemispheres. Dialysate was collected in 20-minute intervals during baseline and following acute administration of increasing doses of nicotine (0.3 then 0.6 mg/kg/base/sc). Following dialysis testing, the samples were quantified for dopamine and GABA levels using liquid chromatography/mass spectrometry procedures.

Results: In females, CRF overexpression in the NAc enhanced baseline and nicotine-induced increases in dopamine levels in the NAc relative to the control hemisphere. There were no changes in GABA levels in the NAc of females. In males, CRF overexpression did not alter baseline or nicotine-induced increases in dopamine relative to the control hemisphere. The blunted nicotine-induced increases in dopamine may have been due to a large increase in GABA levels in males in the NAc.

Conclusions: These findings suggest that CRF systems promote the reinforcing effects of nicotine in females via an enhancement of dopamine transmission in the NAc.