conferenceseries.com
2nd International Conference on
Clinical Trials and Therapeutic Drug Monitoring
August 22-24, 2016 Philadelphia, USA

Kyle Gobrogge et al., J Clin Trials 2016, 6:4(Suppl)
http://dx.doi.org/10.4172/2167-0870.C1.010

Functional identification of a CRF-DA microcircuit in mice with relevance to drug abuse

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Corticotropin releasing factor (CRF) signaling in the posterior ventral tegmental area (pVTA) mediates stress-induced psychostimulant self-administration. Recently, using a Cre-dependent tract-tracing approach with AAV-Flex-ChR2 in adult CRF-Cre male mice, we localized the source of pVTA-CRF to neurons projecting from the lateral hypothalamus (LH) and dorsal raphe nucleus (DRN) synapsing in the paranigral (PN) and parainterfascicular (PIF) sub-nuclei of the ventral posterior medial (VPM) sub-region of the pVTA. We observed that the DRN-, but not the LH-, VPM-CRF circuit was activated after repeated, but not acute, social defeat stress. Furthermore, we found that repeated optical or chemo-genetic activation of CRF in the VPM was sufficient to engender amphetamine (AMPH)-induced-locomotor behavioral cross-sensitization and escalated cocaine intake. Specifically, we observed that male mice with a history of repeated CRF optical or DREADD stimulation in the VPM displayed a significant increase in distance traveled in an open field test after treatment with a low dose of AMPH (1.5 mg/kg) compared to saline treated and Cre-/- littermate controls. Subsequent cocaine self-administration experiments demonstrated that repeated DREADD CRF activation in the VPM enhanced drug-seeking behavior. Here we build upon these data by focusing on the DRN-VPM CRF microcircuit by using a combination of techniques. Previously, we observed site-specific increases in CRF-ir in the PN/PIF but not the parabrachial pigmented area of the pVTA following stress. Thus, we bilaterally infused CRF-Cre male mice with the G(q) DREADD virus into the DRN and implanted a unilateral microdialysis probe aimed at the PN/PIF and sampled the VPM for CRF during saline and CNO treatment. Our data demonstrate enhanced CRF release in the VPM of DREADD G(q) infected DRN-CRF neurons, after i.p. CNO injection. These results suggest functional increases in released CRF in the VPM after activation of DRN-CRF neurons projecting to the pVTA. We will extend this work by measuring dopamine (DA) release in the nucleus accumbens shell of mice with a history of DRN-VPM CRF microcircuit activity. These latter experiments aim to ascertain mesocorticolimbic CRF-DA interactions and potential increases in rate of cocaine self-administration and reinstatement after abstinence. At present, our data reveal a site-specific CRF microcircuit exclusively projecting from the DRN to the VPM sub-region of the pVTA, its sensitivity to social defeat stress, and VPM-CRF release presumably altering DAergic output in the forebrain after repeated experiences with brief episodes of social stress.

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