

Introduction

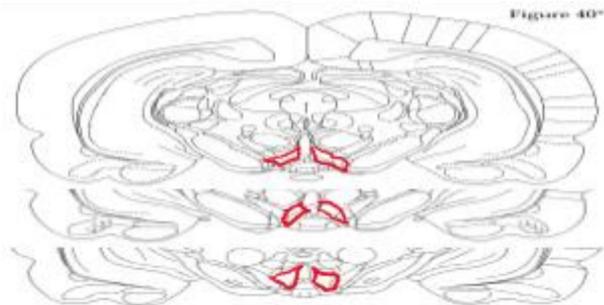
- The interaction between extrahypothalamic stress and dopamine in heroin addiction is not fully understood.
- Rodent models of relapse have shown that corticotropin releasing factor is involved in stress induced relapse, however there is little evidence indicating whether CRF (corticotrophin releasing factor) is involved in heroin self-administration.
- Here, we assessed the effects of CRF sub receptor 1 (CRFR1) blockade in the VTA on heroin self-administration, and whether heroin self-administration alters CRFR1 mRNA expression on dopamine (DA) neurons in the VTA.

Methods

EXPT 1. Male Long evans rats were surgically implanted with intravenous catheters and bilateral intra-VTA steel cannula. Rats were trained to self-administer intravenous heroin under an FR1 schedule of reinforcement in daily 3 hr sessions, until 3 consecutive days of stable heroin intake was met. Following stable intake, rats received intra-VTA antalarmin or vehicle and tested under identical FR1 conditions.

EXPT 2. Male Long evans rats were surgically implanted with intravenous catheters and trained to self administer intravenous heroin under an FR1 schedule of reinforcement. Following 18 days of self-administration, rat VTA sections were processed using an RNAscope *in-situ* hybridization assay.

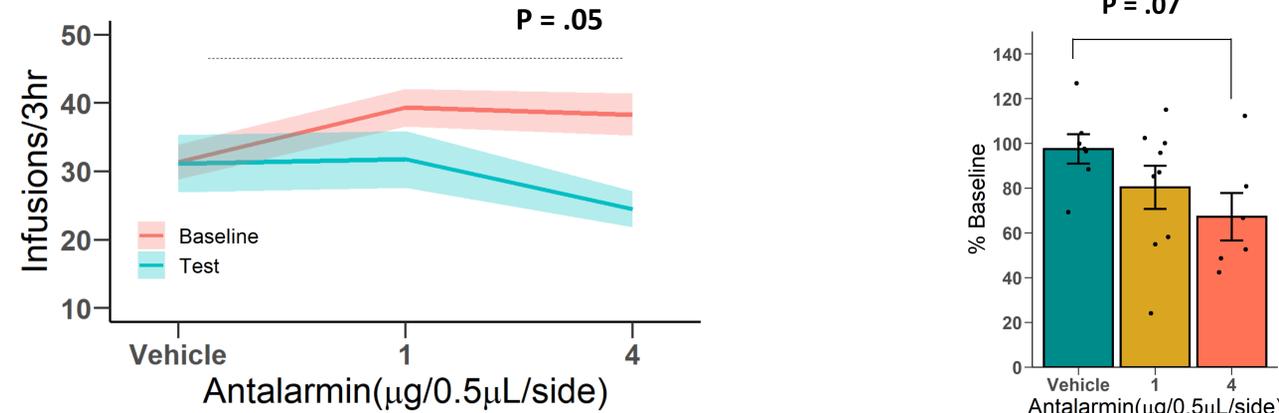
Anatomical coordinates for all experiments



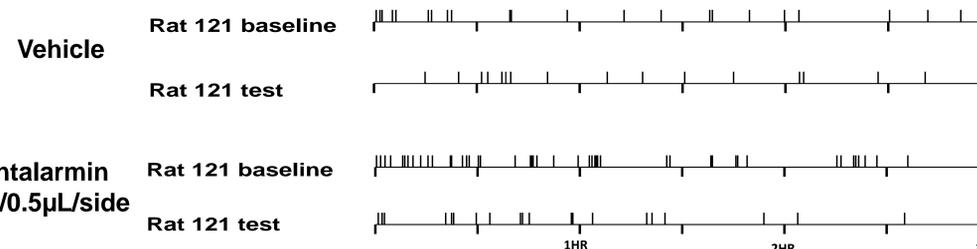
Results

EXPT 1. Intra-VTA injection of CRFR1 antagonist antalarmin attenuates heroin self-administration

A. Heroin infusions during 3hr baseline and test session B. Percent baseline of heroin infusions

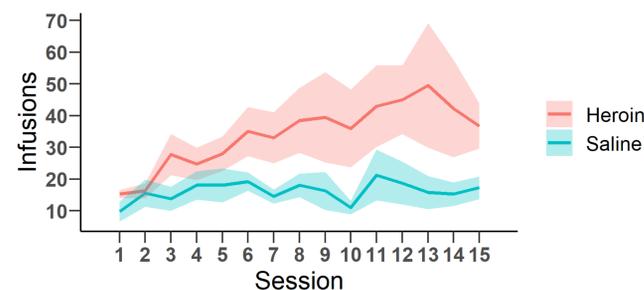


C. Representative event record of heroin intake

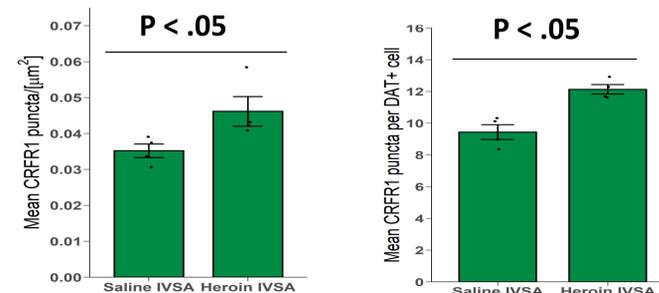


EXPT 2. CRFR1 mRNA is upregulated on VTA dopamine neurons after heroin self-administration

A. Heroin or saline self-administration

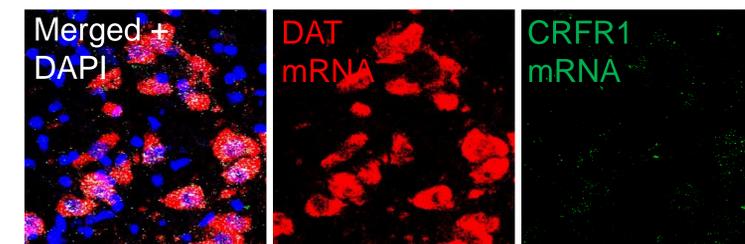


B. Expression of CRFR1 puncta on VTA DA cells

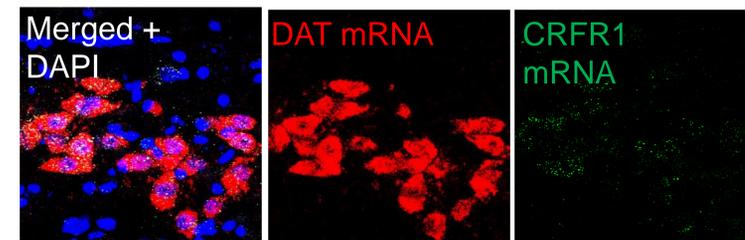


C. Confocal images of VTA nuclei and mRNA

Saline



Heroin



Summary

- CRFR1 blockade in the VTA attenuated heroin self-administration in a dose dependent manner.
- Rats that self-administered heroin for 18 days showed upregulation of CRFR1 on VTA DAT+ neurons when compared to saline controls.

Conclusion

- Our findings suggest that CRF is involved in the rewarding properties of heroin.
- Further, upregulation of CRFR1 on VTA DA neurons may lead to perturbations in DA modulation of mesolimbic terminal areas after heroin exposure. These aberrations may play a role in relapse to heroin.

Future Direction

- Assess the role of CRF during stress induced reinstatement of drug seeking.
- Assess whether CRFR1 protein expression after heroin self-administration corroborates our findings using Western blot assay.