Abstract

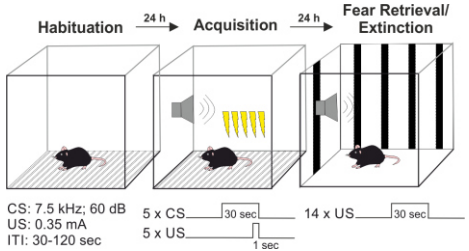
Serotonin (5-hydroxytryptamine, 5-HT) plays a significant role in learning and memory, particularly by its interaction with at least 14 serotonin receptors[1]. The 5-HT$_{2c}$ receptor is involved in the neuronal processing of anxiety, aversive cues and stressors[2].
We used a mouse line devoid of 5-HT$_{2c}$ receptors (5-HT2CR KO) in an auditory fear conditioning paradigm to examine the contribution of this receptor to fear memory and extinction.
Our results reveal that a global lack of 5-HT$_{2c}$ receptors exclusively facilitates fear extinction. This behavioral effect is associated with altered neuronal activity in two distinct brain areas, the dorsal raphe nucleus (DRN) and the bed nucleus of the stria terminalis (BNST), which are both reciprocally connected.

References:

1 López-Vázquez *et al.*, Humana press (The Receptors Series; Springer), vol 22, 2010
2 Règue *et al.*, Translational Psychiatry 9 (1), 2019

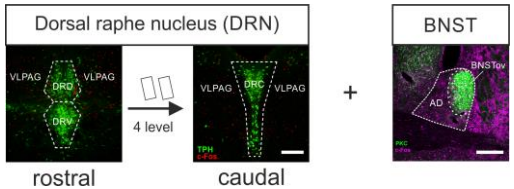
Techniques & Methods

Fear conditioning and fear extinction



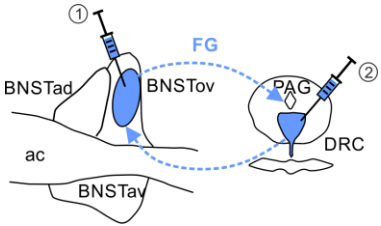
Comparison of 5-HT2CR KO and WT mice

Immunohistochemical (IHC) c-Fos analysis



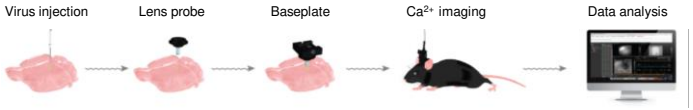
IHC labeling of c-Fos protein as a marker for neuronal activity during fear extinction

Retrograde tracing



Injection of Fluorogold (FG) in bed nucleus of stria terminalis (BNST) or caudal DRN (DRC)

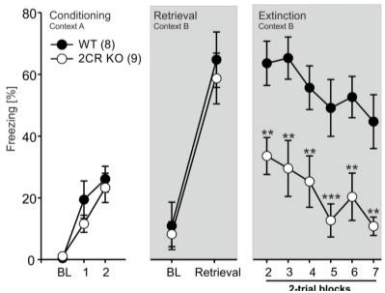
In vivo Ca^{2+} imaging



Viral expression of genetically encoded Ca^{2+} - sensor (GCaMP6m) in serotonergic DRC neurons combined with miniature microscopy (Inscopix)

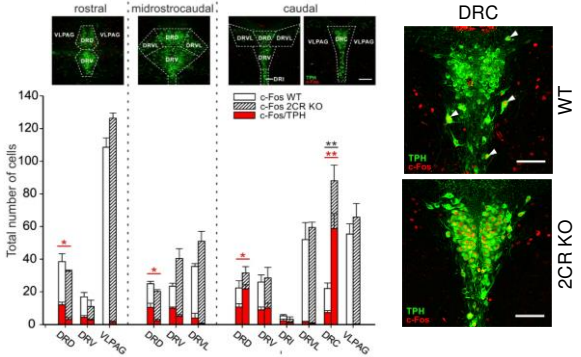
Results

Behavioral analysis

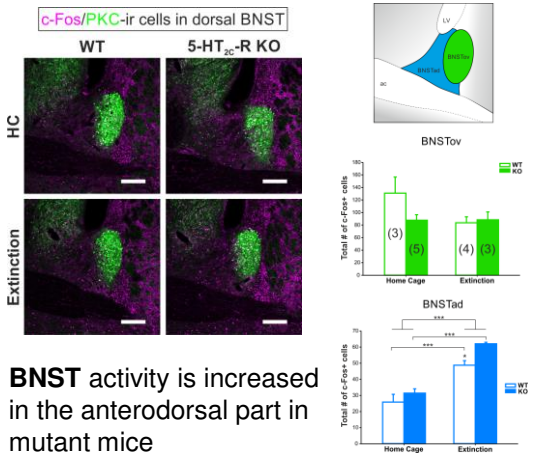


Mutant mice with faster fear extinction

IHC c-Fos analysis after extinction

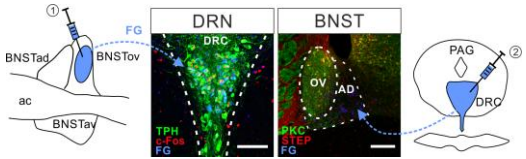


DRN activity is altered in 2 subregions (DRD/ DRC) in mutant mice



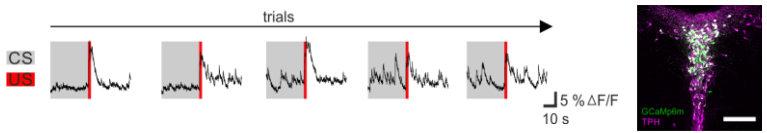
BNST activity is increased in the anterodorsal part in mutant mice

Retrograde FG tracing



DRN (DRC) and BNST are reciprocally connected

In vivo Ca^{2+} imaging



5-HT cells in DRC respond to US during conditioning

Conclusion

Fear extinction facilitation

Global lack of 5-HT$_{2c}$ receptors affects only specific fear related behaviors:

Fear acquisition
Fear retrieval
→ not affected

Fear extinction
→ affected

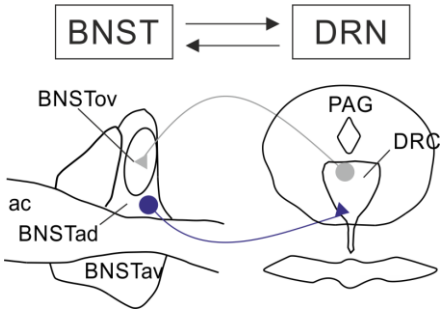
Changes in neuronal activity

Faster fear extinction is associated with altered neuronal activity in two brain regions:

Dorsal raphe nucleus
→ DRD/DRC affected

Bed nucleus of the stria terminalis
→ BNSTad affected

Reciprocal connected areas



Alterations of DRN-BNST circuit may lead to faster fear extinction