The role of sex hormones and gene expression in membrane properties of the vHPC to BLA circuit in anxiety expression

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ABSTRACT

- Lack of circuit-based molecular understanding of neurobiology underlying anxiety is a key roadblock in development of effective treatments for anxiety disorders.
- To study the role of the ventral hippocampus (vHPC) projections to basolateral amygdala (BLA) in anxiety, I will create circuit-specific gene knock outs using genetic tools and test electrophysiological outcomes.
- I hypothesize that decreased anxiety-like behaviors will be correlated with increased excitability of vHPC-BLA neurons whereas increased anxiety-like behaviors will be associated with decreased excitability, and that these effects will be dependent on expression of ΔFosB and androgen receptors (AR).

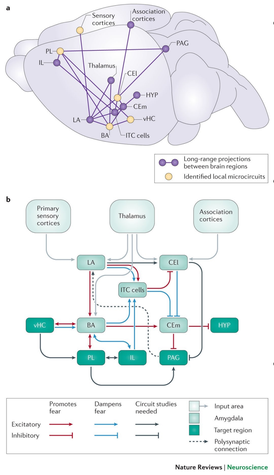


Figure 1: **Neural circuitry of fear.** Previous research does not show the cellular basis of the functioning of neural circuits important in fear and anxiety (Tovote *et al*, 2015).

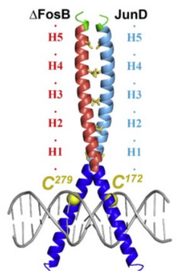


Figure 2: ΔFosB and JunD dimer function. Important in mediating susceptibility to stress, learning, and overall key modulator of vHPC function (Yin *et al*, 2020). Its expression in the vHPC to BLA circuit is required for anxiety-like behaviors (Eagle *et al*, 2020).

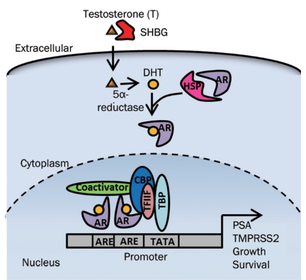
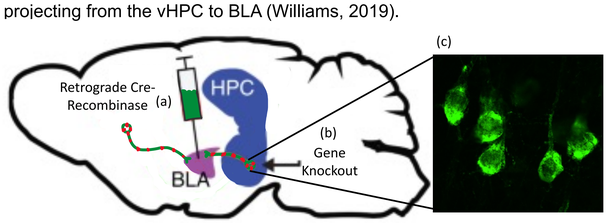


Figure 3: Cellular function of the androgen receptor. Important in testosterone signaling and could have a role in sex-based differences in anxiety (Tan *et al,* 2015).

CIRCUIT MANIPULATIONS

Figure 5: Circuit based manipulation of the vHPC to BLA circuit. (a) Retrograde virus containing Cre-recombinase infused into the BLA. (b) Cre-dependent conditional knockout (cKO) of gene in cells projecting form the vHPC to BLA with a GFP reporter. (c) Representative GFP cells projecting from the vHPC to BLA (Williams, 2019).



ELECTROPHYSIOLOGICAL DIFFERENCES IN vHPC-BLA- BUILDING FROM PREVIOUS WORK

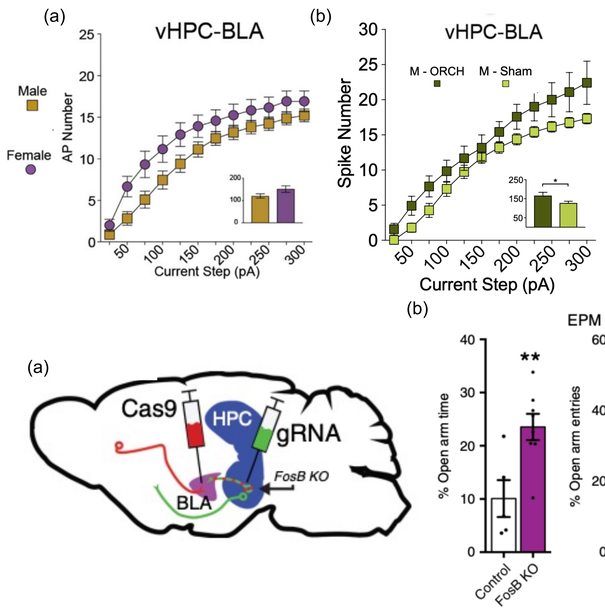


Figure 6: Excitability of male (orchiectomized or sham) and female vHPC-BLA circuits. (a) There is no statistical difference in excitability within the vHPC-BLA circuit in males and females ($p>0.05$) (Williams *et al*, 2020). (b) Williams also found that orchidectomy treated (ORCH) male mice also displayed an increased excitability as evidenced by the greater total number of spikes in the ORCH group compared to Sham controls ($p<0.05$).

Figure 7: ΔFosB is required for anxiety-like behaviors within the vHPC to BLA circuit. (a) Circuit specific knockout (KO) of ΔFosB. (b) Male KO mice spend significantly more time in the open arms. (c) KO mice have impaired avoidance learning with fear conditioning (Eagle *et al*, 2020).

ELECTROPHYSIOLOGY RESULTS

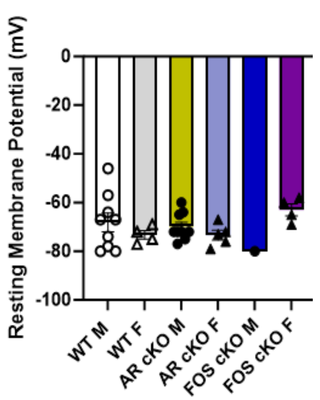


Figure 8: Resting membrane potential of neurons in the vHPC to BLA circuit. There are no differences in resting membrane potential between groups.

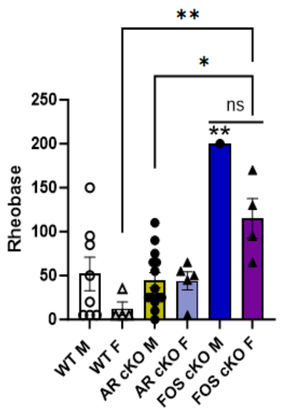


Figure 9: Rheobase of neurons in the vHPC to BLA circuit. There is a significant increase in current required to reach threshold in the FOS cKO M group compared to all except the FOS cKO F group ($p<0.01$). Also, FOS cKO F required significantly more current to reach threshold compared to the WT F and AR cKO groups ($p<0.05$).

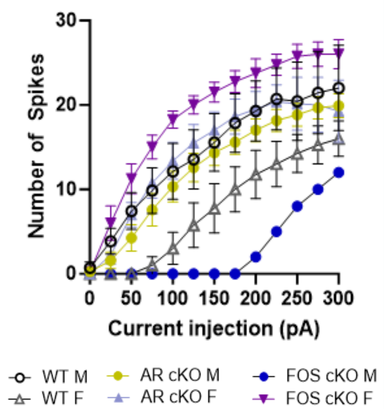
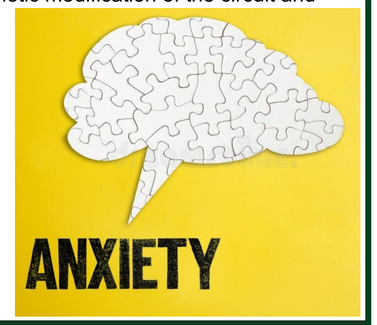


Figure 10: Excitability of neurons in the vHPC to BLA circuit. There are no differences in excitability between groups.

CONCLUSIONS

- Further investigation into the neuronal basis of anxiety is required.
- I plan to continue a cellular analysis of the vHPC to BLA circuit that includes sex-based, gene-based (KO of ΔFosB, calreticulin, and androgen receptor), and chemogenetic modification of the circuit and exploration of the effect on anxiety-like behaviors.
- I will further examine the electrophysiological differences that each genetic modification of the circuit provides.
- Results from this experiment may provide pharmacological targets for drug development targeted to the vHPC to BLA circuit.



NEXT STEPS

- Sub-chronic variable stress (SCVS) is a paradigm defined by variable presentation of three stressors- tail suspension, foot shock, and restraint- daily for one hour over six days.
- Anxiety and mood behaviors will be assessed using elevated plus maze, open field test, social interaction test, fear learning, sucrose preference, and novelty suppressed feeding.

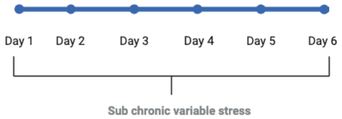


Figure 11: Stressors in both SCVS and CVS. From left to right: foot shock, tail suspension, and restraint stress.

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