

BACKGROUND

There is high co-morbidity between obesity and mental diseases, such as depression, anxiety, and ADHD¹. AgRP neurons in the arcuate nucleus (ARC) are pivotal for the regulation of appetite and body weight by projecting to targets distributed in the hypothalamus and brainstem. Evidences also implicated association of AgRP neurons with a wide variety of cognitive activities such as anxiety, stereotypic behaviors and motivation²⁻³. Several limbic and frontostriatal neural circuits were recently revealed for the control of mood disorders. However, the neural circuits and key signaling mechanisms underlying the association of feeding and mental states are unclear.

PURPOSE

Verify neural circuits that regulate feeding and mental dysfunctions. Evaluate FDA-approved drugs combination for attenuation of obesity and anxiety/depression in mice.

METHODS

- Brain Surgery and Viral Injections
- Pharmacology
- Food Intake and Body Weight
- Open Field Test
- Elevated Plus Maze Test
- Forced Swim Test
- Tail Suspension Test
- Marble Burying Test
- Optogenetics
- *In Vivo* Fiber Photometry
- Fluorescence-activated cell sorting (FACS)
- Immunohistochemistry
- AgRP Neurons Ablation and Counting
- Quantitative real-time PCR
- *In vitro* electrophysiological recordings
- Anterograting/retrograding tracing
- Circuits mapping

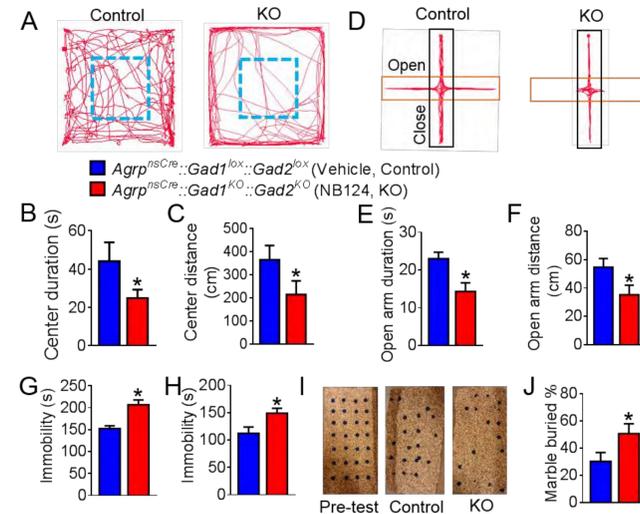


Fig 1: Figure 1. Acute inactivation of GABA signaling from AgRP neurons induces anxiety-like behaviors and depression-like behaviors.

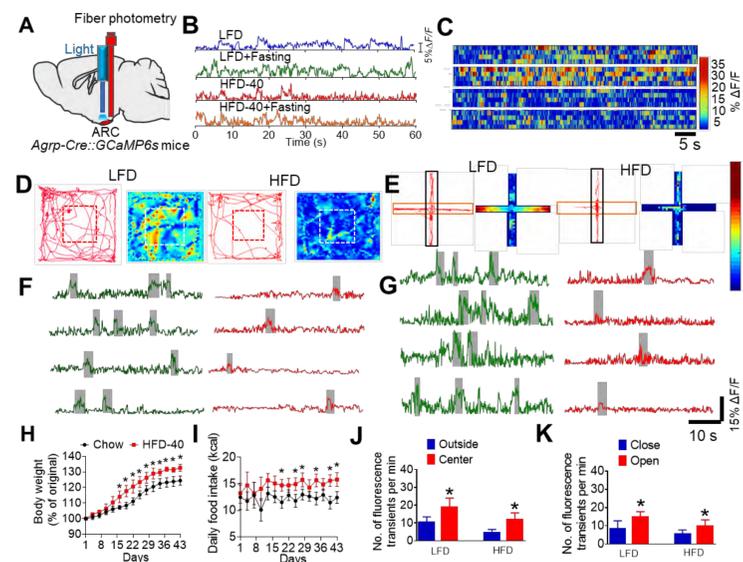


Fig 2: AgRP neural activity dynamics during HFD feeding and behavior paradigms.

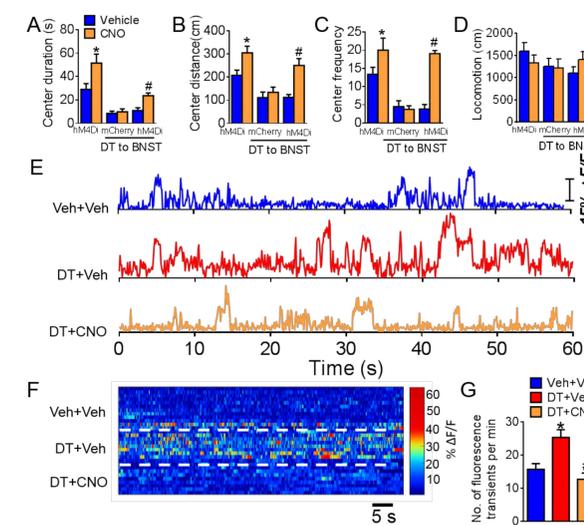


Fig 3: MC4R^{dBNST} neurons mediate anxiety-like behaviors and depression-like behaviors

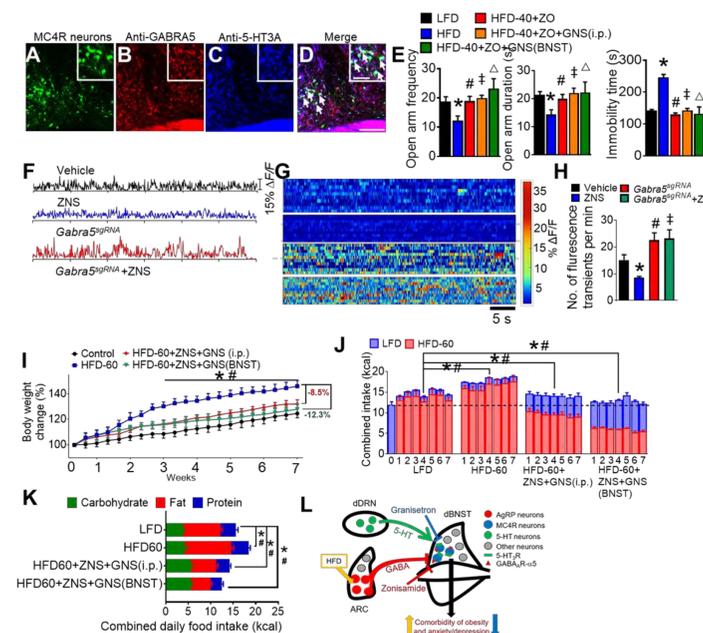


Fig 4: Pharmacological manipulations of MC4R^{dBNST} neurons attenuate obesity and its mental comorbidity.

RESULTS

- Rapid inactivation of their GABA biosynthesis induces anxiety and depression-like behavior
- Photostimulation of the AgRP^{ARC}-BNST circuit significantly enhances the anxiety and depression level, whereas chemogenetic activation of the MC4R^{dBNST} neurons leads to opposite responses
- Mental dysfunctions caused by ablation of the AgRP^{dBNST} neurons are completely restored by chemogenetic silencing the MC4R^{dBNST} neurons
- Suppression of the 5-HT₃R signaling in the dBNST or inactivation of the 5-HT^{DRN}-dBNST pathway abolishes the anxiety and depression-like behavior in the AgRP^{ARC}-dBNST ablation model
- Deletion of Gabra5 within the MC4R^{dBNST} neurons causes severe anxiety and depression, which is completely rescued by genetic suppression of the 5HT₃R receptor
- Inactivation of MC4R neurons or overexpression of GABA_A $\alpha 5$ receptor in dBNST rescues anxiety-like behavior and depression-like behavior induced by HFD
- Genetic disruption of Htr3a or overexpression of Gabra5 in MC4R^{dBNST} neurons causes late-onset decrease of body weight by switching food preference toward low-calorie diets.

CONCLUSION

In summary, our findings reveal a novel neural circuit that exerts a reciprocal control of body weight and mental states by converging GABAergic signaling from AgRP neurons and serotonergic signaling from the dDRN onto MC4R^{dBNST} neurons that co-express $\alpha 5$ -containing GABA_AR and 5-HT₃A receptors.

REFERENCES

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2. Wu, Q., Clark, M. S. & Palmiter, R. D. Deciphering a neuronal circuit that mediates appetite. *Nature* 483, 594-597 (2012).
3. Dietrich, M. O., Zimmer, M. R., Bober, J. & Horvath, T. L. Hypothalamic AgRP neurons drive stereotypic behaviors beyond feeding. *Cell* 160, 1222-1232 (2015).