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Research Advance

Hyperactivity of a midbrain dopamine to 5-HT circuit causes anorexia

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Anorexia nervosa (AN) is a severe eating disorder that can eventually lead to death, but effective therapies are missing due to a lack of knowledge about its pathophysiology. Dopamine (DA) neurons in the ventral tegmental area (VTA) and serotonin (5-HT) neurons in the dorsal Raphe nucleus (DRN) play essential roles in the control of eating and have been reported to be associated with human AN (Zhou and Palmiter, 1995; Xu et al., 2017; Watson et al., 2019; He et al., 2021). However, this association has not been validated in animal models. In addition, how DA and 5-HT neurons interact with each other to contribute to the pathology of AN remains to be elucidated.

In our recent publication (Cai et al., 2022), we demonstrated that DA^{VTA} neurons regulate the activity of $5\text{-}HT^{DRN}$ neurons in a strength-dependent manner. DA receptors D1 (DRD1) and D2 (DRD2) are co-expressed in a sub-population of $5\text{-}HT^{DRN}$ neurons. DRD1 is a Gαs-coupled excitatory receptor that can be activated by high levels of DA (Kern et al., 2015). On the other hand, DRD2 is a Gαi-coupled inhibitory receptor that has high affinity to DA when its concentration is low (Richfield et al., 1989). These opposite features of the two DA receptors permit bi-directional regulation of 5-HT neurons by DA. Indeed, while low-frequency (2 Hz) tonic firing of DA^{VTA} neurons inhibits $5\text{-}HT^{DRN}$ neurons via DRD2 and promotes feeding, high-frequency (20 Hz) phasic bursting of DA^{VTA} neurons activates $5\text{-}HT^{DRN}$ neurons via DRD1 and suppresses feeding.

We further revealed that hyperactivity of the DA^{VTA} to $5\text{-}HT^{DRN}$ circuit underlies the AN-like behaviors through a widely used rodent model for AN, activity-based anorexia (ABA), a paradigm comprised of unlimited access to a running wheel and restricted feeding (Figure 1). In this ABA model that resembles human AN, the DA and 5-HT neuronal activities were constantly elevated. Deletion of *Drd2* in the DRN resulted in no significant changes in feeding and physical activity when mice were suffering from ABA. By contrast, inhibition of the DA^{VTA} to $5\text{-}HT^{DRN}$ circuit or blocking the function of DRD1 in the DRN could partially rescue the AN phenotypes. Therefore, our findings shed light on developing therapeutic strategies against AN by targeting DRD1.

Despite the breakthrough discovery on the DA^{VTA} to $5\text{-}HT^{DRN}$ neural circuit in mediating the AN-like behaviors, there remain some challenges. For example, $5\text{-}HT^{DRN}$ neurons also receive local gamma-aminobutyric acid (GABA) inputs from the DRN. Whether and how these $GABA^{DRN}$ neurons participate in the development of AN requires exploration. Additionally, women are more prone to AN, but whether there is a sex-dependent effect of the DA^{VTA} to $5\text{-}HT^{DRN}$ circuit on feeding regulation remains unclear. Moreover, 5-HT system has

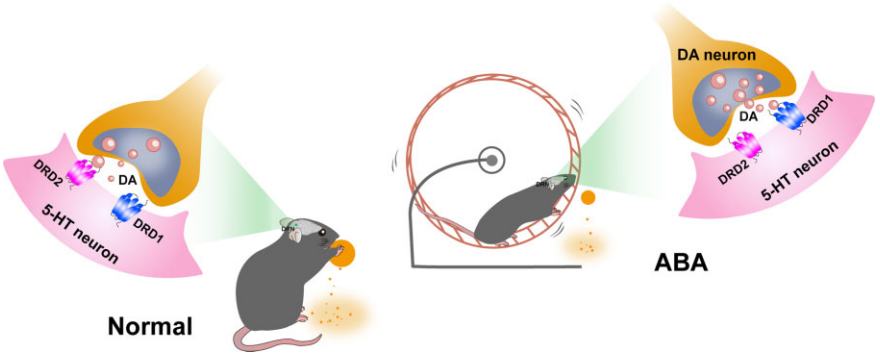

Figure 1 Low-frequency tonic firing of DA^{VTA} neurons inhibits $5\text{-}HT^{DRN}$ neurons via DRD2-mediated neurotransmission in normal control mice to promote feeding, whereas high-frequency phasic bursting of DA^{VTA} neurons activates $5\text{-}HT^{DRN}$ neurons via DRD1-dependent mechanisms to suppress feeding behavior in the ABA mouse model.

emerged as a promising target for a number of metabolic and psychiatric diseases, including obesity, anxiety, and depression (Daut and Fonken, 2019; van Galen et al., 2021). Given that a subset of DA^{VTA} neurons can project to and bi-directionally modulate the activity of $5\text{-}HT^{DRN}$ neurons, it would be of interest to test whether such behaviors can also be bi-directionally controlled by the DA^{VTA} to $5\text{-}HT^{DRN}$ circuit in a strength-dependent manner.

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References

Cai, X., Liu, H., Feng, B., et al. (2022). A D2 to D1 shift in dopaminergic inputs to midbrain 5-HT neurons causes anorexia in mice. Nat. Neurosci. *25*, 646–658.

Daut, R.A., and Fonken, L.K. (2019). Circadian regulation of depression: a role for serotonin. Front. Neuroendocrinol. *54*, 100746.

He, Y., Cai, X., Liu, H., et al. (2021). 5-HT recruits distinct neurocircuits to inhibit hunger-driven and non-hunger-driven feeding. Mol. Psychiatry *26*, 7211–7224.

Kern, A., Mavrikaki, M., Ullrich, C., et al. (2015). Hippocampal dopamine/DRD1 signaling dependent on the ghrelin receptor. Cell *163*, 1176–1190.

Richfield, E.K., Penney, J.B., and Young, A.B. (1989). Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. Neuroscience *30*, 767–777.

van Galen, K.A., Ter Horst, K.W., and Serlie, M.J. (2021). Serotonin, food intake, and obesity. Obes. Rev. *22*, e13210.

Watson, H.J., Yilmaz, Z., Thornton, L.M., et al. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat. Genet. *51*, 1207–1214.

Xu, P., He, Y., Cao, X., et al. (2017). Activation of serotonin 2C receptors in dopamine neurons inhibits binge-like eating in mice. Biol. Psychiatry *81*, 737–747.

Zhou, Q.Y., and Palmiter, R.D. (1995). Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. Cell *83*, 1197–1209.