RESEARCH HIGHLIGHT

Physical activity controlled by estrogen signals in the medial amygdala

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Estrogen receptor α (ERα) in the brain is known to influence different aspects of energy balance in both sexes. However, the essential brain ERα sites for the estrogenic control of body weight have not been fully illustrated. In a recent paper published in the Journal of Clinical Investigation, we demonstrated that ERα expressed in the brain medial amygdala (MeA), which is originally recognized as an important emotion and motivation control center, is required to stimulate physical activity. Our results from both selective deletion or overexpression mouse model and electrophysiology recordings support a model that ERα activates MeA neurons to enhance physical activity and prevent obesity. These results indicate that MeA ERα is a potential target for treatment of obesity.

Keywords: ERα; MeA; physical activity; body weight

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ERα mediates estrogenic effects on energy balance

Both human and rodent studies demonstrated that the ovarian hormone, estrogen, produces important anti-obesity and anti-diabetic effects by regulating feeding, physical activity, heat production, fat distribution and insulin sensitivity[1-8]. A series of studies carried out in two types of ER knockout mice showed that the primary mediating receptor for the estrogenic regulation on energy balance is ERα, but not ERβ. ERα knockout mice have increased body weight, hyperadiposity, hypoactivity and altered glucose homeostasis [9-11], while ERβ knockout mice have normal body weight[12]. Importantly, in 2011, we demonstrated that the estrogenic effect on energy homeostasis requires brain ERα [13]. Mice with a brain-specific deletion of ERα develop obesity associated with hyperphagia, decreased heat production, and hypoactivity. Consequently, we aimed to anatomically dissect the essential ERα sites in the brain for body weight control. We showed that ERα expressed by pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus regulates food intake, while ERα in the ventral medial hypothalamus modulates heat production in females [13]. Although the ERα sites mediating estrogenic regulation of food intake and heat production are defined, little is known about the ERα neural circuits regulating of physical activity.

ERα in the medial amygdala regulates physical activity

ERα is abundantly expressed in an extra-hypothalamic brain region, the medial amygdala (MeA). Previous studies have showed that local injection of 17β-estradiol into the amygdala decreases body weight in rats. Additionally, early lesion [14, 15] and pharmacological [16,17] studies suggest that the amygdala is involved in the control of physical activity. These findings suggest that ERα in the MeA may influence physical activity. In a recent paper published in Journal of Clinical Investigation, we used loss-of-function and

gain-of-function mouse models to systemically test the physiological relevance of MeA ERα in the control of energy homeostasis. We first examined brain regions that co-express ERα and a transcription factor, single-minded-1 (SIM1). We found that the most abundant SIM1-expressing ERα neurons are located in the MeA (80%). Subsequently, we deleted the Esr1gene (encoding ERα) only in SIM1-expressing neurons (SIM1-ERα-KO). When fed with regular chow, SIM1-ERα -KO mice, regardless males or females, developed late-onset obesity associated with reduced energy expenditure and physical activity, while food intake was not altered. Notably, when fed on a high-fat diet (HFD), male SIM1-ERα-KO mice were prone to diet-induced obesity (DIO), while females were not. The dramatic sexual dimorphism in response to HFD feeding may be attributed to the stronger redundant metabolic relevant circuits in female brains than in male brains. While multiple ERα-expressing sites in female brains contribute to body weight balance, the MeA is the only ERα site identified so far that is essential for energy homeostasis in males.

To further specifically characterize MeA ERα metabolic functions, we stereotaxically inject AAV-Cre-GFP into the MeA of $Esr1^{fl/fl}$ mice or mice carrying a Cre-dependent human Esr1 overexpression allele, which resulted in deletion of Esr1 (MeA-ERα-KO) or overexpression of human Esr1 (MeA-ERα-OE) specifically in the MeA. We found male MeA-ERα-KO mice showed a rapid body weight gain and marked decreases in physical activity, while food intake did not change. On the other hand, male MeA-ERα-OE mice were partially protected from DIO. These findings indicate that MeA ERα plays physiologically relevant roles in the regulation of physical activity and body weight.

Additionally, using electrophysiology, we demonstrated that an ERα agonist, propyl pyrazole triol (PPT), activated MeA SIM1 neurons in an ERα-dependent manner. Further, selective stimulation of MeA SIM1 neurons resulted in a transient but significant increase in physical activity in mice. These findings suggest that ERα activates MeA SIM1 neurons to enhance physical activity.

Conclusions

Our results identified one ERα site in the brain that is important for physical activity control for not only females but also males. The understanding of physical activity regulation by MeA/ERα circuits provides a potential pharmacological space for controlling body weight through targeting sedentary behavior in humans.

Future directions include identifying the critical neurotransmitters and the neural circuits downstream of MeA ERα neurons that are important for the regulation of physical activity. We also aim to further genetically dissect other essential neuron populations involved in ERα-mediated regulations on energy balance. We hope these efforts will advance our understanding about estrogenic control of body weight and provide more rational targets for the developments of new estrogen based therapies.

Conflicting interests

The authors have declared that no competing interests exist.

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