Estrogen Signaling in the Ventromedial Hypothalamus Modulates Adipose Tissue Metabolic Adaptation

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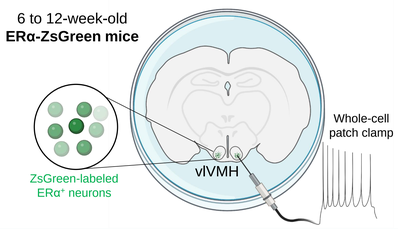
Abstract

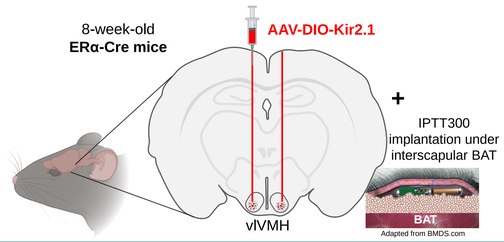
Brain estrogen receptor α (ERα) signaling plays a vital role in the regulation of energy homeostasis and adipose tissue metabolism. It has been demonstrated that ERα is abundantly expressed in the ventrolateral region of the ventromedial hypothalamus (vlVMH), a sex-dimorphic structure that directly modulates brown adipose tissue (BAT) thermogenesis. Despite the abundant evidence supporting the role of ERα^{vlVMH} in energy expenditure and metabolic function, *it is still unclear whether ERα^{vlVMH}-originated networks respond to environmental challenges, subsequently regulating adipose tissue metabolic adaptations*. Here, we found that an ERα^{vlVMH}-originated neural circuit responds to changes in ambient temperature and nutritional states, suggesting thermo- and nutrient-sensing properties and a potential role in metabolic adaptation. In line with this, selective activation of ERα^{vlVMH} stimulates physical activity, increases BAT thermogenesis, and reduces body weight gain. Conversely, chronic inhibition of ERα^{vlVMH} neurons increases body weight and adiposity and decreases baseline (22°C) BAT temperature. Notably, inhibition of these neurons also impairs cold-induced food consumption and BAT thermogenesis, resulting in lethal phenotypes during chronic cold exposure. Post hoc histology analysis further revealed that ERα^{vlVMH} neurons inhibition induces adipose tissue whitening. Together, these findings support a model that **estrogens act through ERα^{vlVMH} neurons to modulate fat-specific outputs and subsequently regulate adipose tissue adaptation to cold challenges**.

Methodology

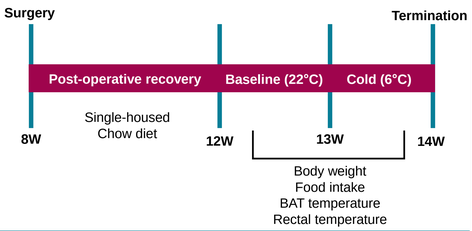
Electrophysiological response of ERα^{vlVMH} neurons



Generation of ERα Kir2.1^{vlVMH} (inhibition model)



Experimental Timeline



Results

Figure 1. ERα^{vlVMH} neurons respond to changes in ambient temperature and nutritional states in female mice*

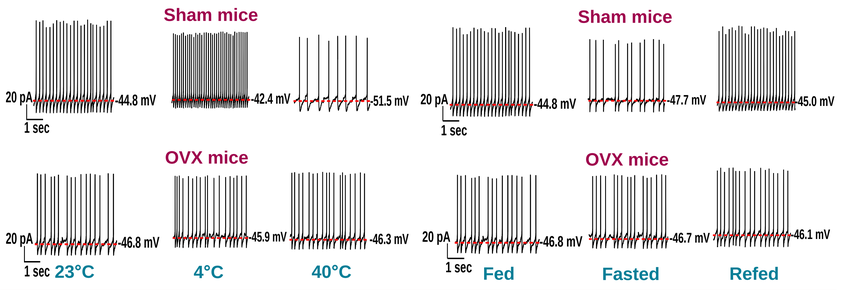


Figure 2. Chemogenetic activation of ERα^{vlVMH} neurons stimulates physical activity and BAT thermogenesis in females*

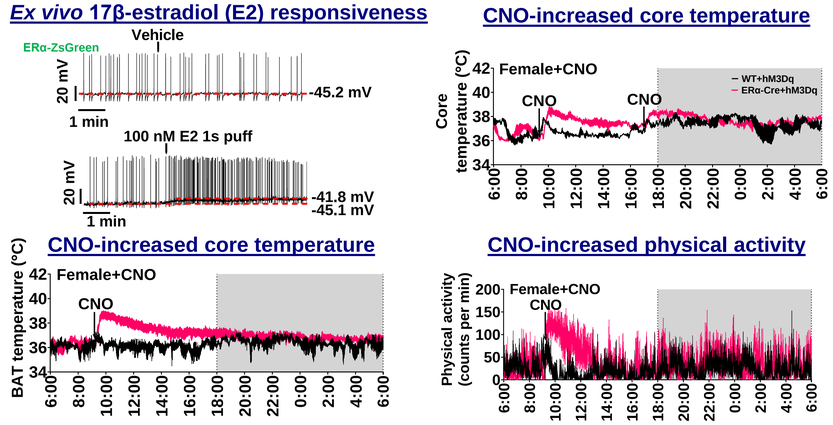


Figure 3. Chronic inhibition of ERα^{vlVMH} neurons increases baseline (22°C) body weight and adiposity

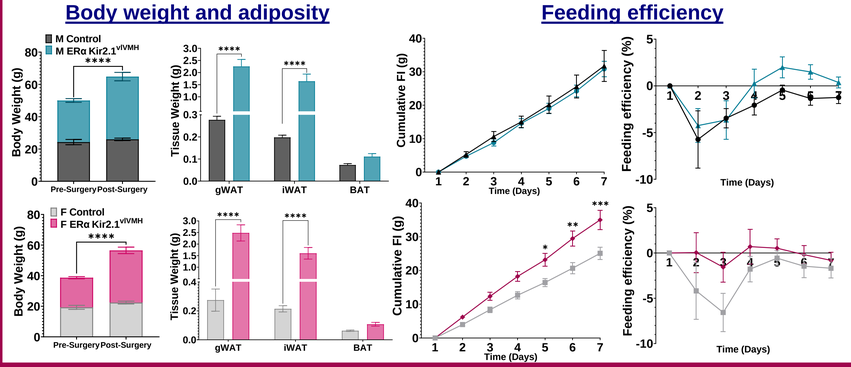


Figure 4. Chronic inhibition of ERα^{vlVMH} neurons decreases baseline (22°C) BAT and rectal temperature

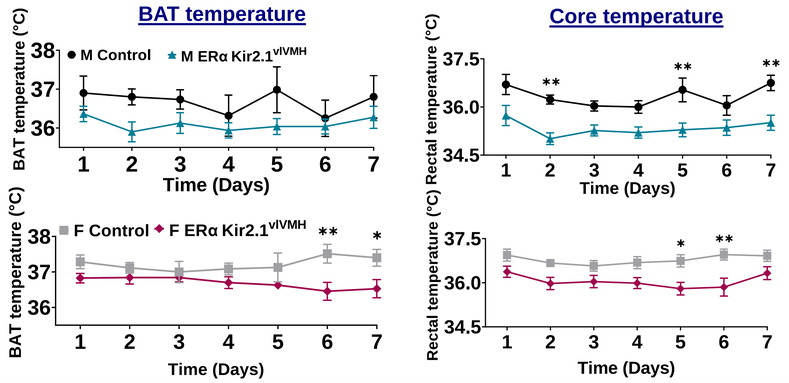


Figure 5. Chronic inhibition of ERα^{vlVMH} neurons impairs cold-induced (6°C) food consumption

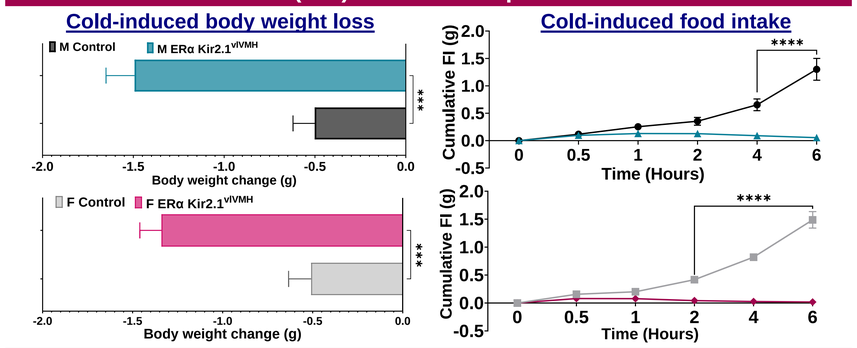


Figure 6. Cold exposure impairs BAT thermogenesis and survival rate in ERα^{vlVMH} mice

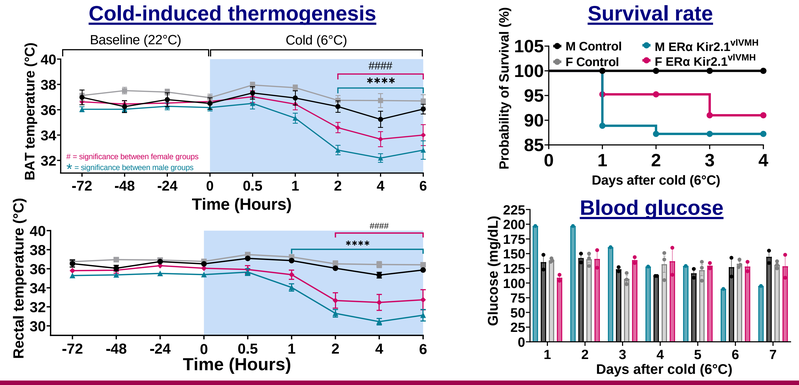
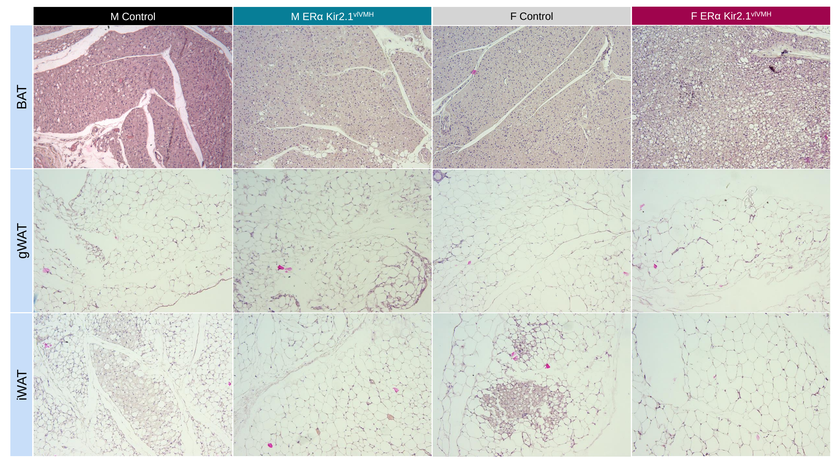
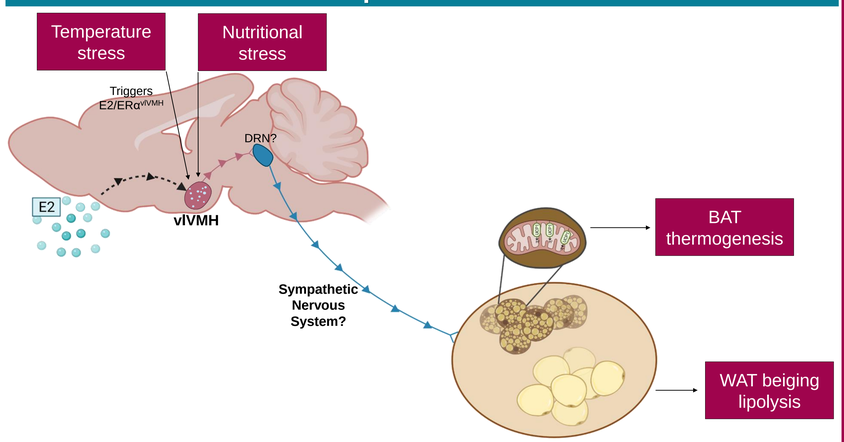


Figure 7. ERα^{vlVMH} inhibition induces adipose tissue whitening



Proposed Model



Estrogen acts through ERα^{vlVMH}-originated circuits to modulate fat-specific sympathetic outputs and subsequently regulate adipose tissue adaptation to environmental challenges

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