Control of adipose tissue inflammation by hypothalamic SF1 neurons

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Obesity is a complex disorder that is strongly linked to a sedentary lifestyle and insufficient physical activity. When total energy intake exceeds total energy expenditure, body weight increases and leads to many metabolic diseases, including cardiovascular disease, non-alcoholic fatty liver disease, and type 2 diabetes mellitus. Following high-fat diet (HFD) consumption, adipose tissues accommodate the high amount of free fatty acid by increasing the size and number of adipocytes. Such remodeling of adipocytes during obesity is marked by dysfunctional adipose tissue that is accompanied by inflammation. Adipose tissue inflammation is characterized by the accumulation of pro-inflammatory macrophages and the secretion of inflammatory cytokines.

The hypothalamic ventromedial nucleus (VMH) plays a crucial role in the regulation of body weight and adiposity and is one of the important brain regions to regulate energy balance. Steroidogenic factor 1-expressing neurons (SF1 neurons) in the VMH play an essential role in controlling energy metabolisms of peripheral tissues, including brown adipose tissue (BAT) and white adipose tissue (WAT). Various previous studies revealed the roles of SF1 neurons in BAT thermogenesis, WAT browning, and resistance to diet-induced obesity. However, whether obesity-induced

inflammatory responses in adipose tissues are regulated by SF1 neurons remains unclear.

In this study, I investigated the roles of SF1 neurons in the inflammatory responses in HFD-induced obese mice. To accomplish this, I modulated SF1 neurons in the VMH and investigated inflammatory responses in adipose tissues, as well as the changes in energy metabolism.

First, I ablated SF1 neurons in the VMH by injecting adeno-associated viruses (AAVs) with Cre recombinase-dependent diphtheria toxin-A (DTA) expression into SF1-Cre mice. In the absence of SF1 neurons, I found that body weight was increased without affecting food intake when mice were fed with HFD for 8 weeks. Both total and basal energy expenditure and locomotor activity during the dark phase were decreased in the mice without SF1 neurons. SF1 neuron-ablated mice showed glucose intolerance and lipid oxidation impairment. These results indicate that VMH-specific SF1 neuron ablation led to metabolic complications during HFD feeding compared to control mice.

Notably, ablation of SF1 neurons aggravates obesity-induced inflammatory responses in specific adipose tissues. I found that expression of macrophage markers and inflammatory cytokines was substantially increased in inguinal white adipose tissue (ingWAT) but not in not in epididymal WAT (epiWAT) in HFD-fed obese mice. Immunohistochemistry and transcriptome analysis of ingWAT confirmed these findings, revealing that SF1 neuron ablation enhanced the expression of many inflammation-related genes. Ablation of SF1 neurons significantly decreased the expressions of thermogenesis and mitochondria-related genes as well as increased the gene expressions of macrophage markers in BAT in these mice.

These results suggest that SF1 neuron ablation in the VMH exacerbates HFD-induced inflammatory responses in ingWAT and thermogenic function in BAT but had little effect in epiWAT. Thus, the effects of SF1 ablation are dependent on the type of adipose tissues.

Next, I examined whether SF1 neurons played a role in ameliorating obesity-induced inflammatory responses upon activation. I activated SF1 neurons by a chemogenetic method known as designer receptors exclusively activated by designer drugs (DREADD). Chemogenetic receptor hM3Dq, when expressed in neurons, can activate neurons in the presence of a specific ligand, clozapine-N-oxide (CNO). I used AAV to selectively express hM3Dq in SF1 neurons in SF1-Cre mice and administered CNO through drinking water. These mice were fed with HFD for 4 weeks along with CNO to achieve simultaneous activation of SF1 neurons and obesity development. Mice with chronic activation of SF1 neurons showed a similar body weight increase and food intake when compared with control mice. However, the chronic activation of SF1 neurons substantially suppressed the gene expressions of inflammatory cytokines and macrophage markers in ingWAT but not in epiWAT in HFD-fed obese mice. Intriguingly, the expressions of thermogenesis and mitochondria-related genes in BAT were significantly increased by the chronic activation of SF1 neurons.

Finally, I examined whether chronic activation of SF1 neurons suppresses HFD-induced inflammatory response in ingWAT in mice that already developed obesity before stimulation of the SF1 neurons. Mice were first fed with HFD for 8 weeks without stimulation of SF1 neurons and then SF1 neurons in the VMH were activated for 4 weeks by CNO administration with continued HFD feeding. Even under this condition, the chronic

activation of SF1 neurons reduced the inflammatory gene expressions in ingWAT. These results suggest that chronic activation of SF1 neurons suppresses inflammatory responses in adipose tissue in mice that already developed obesity.

Overall, these findings indicate that SF1 neurons play a critical role in controlling inflammatory responses in specific adipose tissues in HFD-fed obese mice, in addition to their roles in the regulation of the body weight, lipid, and glucose metabolism. These findings demonstrate that SF1 neurons in the VMH mitigate the obesity-induced inflammatory responses differently in various adipose tissues and provide the first evidence to reveal a connection between the VMH and inflammatory responses in the adipose tissues.