Exercise improves hypothalamic dysfunction induced by high-fat diet

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High-fat Diet (HFD) induced obesity is known as a model of mostly closed to human obesity condition. Diet-induced obesity (DIO) not only induces peripheral insulin resistance and glucose intolerance but also impairs central leptin and insulin signaling pathways. Exercise training reduces adiposity by mainly increased energy expenditure, however, the underlying mechanism associated with central nervous system remains largely unknown. This article highlights the recent publication by Laing et al., who first demonstrated that voluntary exercise enhanced POMC-expressing neuron survival rate in the hypothalamus of mice by protecting from apoptosis induced by long-term HFD induced obesity, improved central leptin sensitivity, and systemic insulin sensitivity, to shed a light on the central mechanism of exercise to improve metabolic function.

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Introduction

Obesity directly impacts 80 million Americans and is a significant driver of medical costs [1]. Imbalanced energy intake and energy expenditure contribute to obesity, with both parameters under profound influence from the Central Nervous System [2]. The arcuate nucleus of the hypothalamus of the brain houses a population of pro-opiomelanocortin (POMC) expressing neurons which drive satiety and energy expenditure. Activation of POMC-expressing neurons results in suppressed food intake and increased energy expenditure [3], while genetic ablation of POMC-expressing neurons is sufficient to increase body weight and adiposity. Exercise training is well known as an alternative treatment, at least in part, by changes in the regulation of whole-body energy homeostasis which counter increased body weight from energy surplus associated with obesity [4]. Emerging evidence suggests that high-fat diet induced neuronal damage and loss occurs preferentially in the arcuate of hypothalamus, such as in POMC-expressing neuron [5]. The neural benefits of exercise associated energy expenditure are incompletely understood. Using exercise in combination with diet-induced obesity (DIO) to test the effects of exercise training on arcuate nucleus turnover and function, Laing et al. demonstrated arcuate specific neuroprotective benefits which occur in concordance with whole body and
organ system level adaptations in response to voluntary exercise-induced energy expenditure \[6\].

**Neuroprotective effects of voluntary exercise in HF DIO mice**

Substantial evidence points to the beneficial effects of exercise on the central nervous system. There is clear evidence of beneficial exercise-induced neural adaptations in Alzheimer’s disease \[7\], ischemic stroke \[8\], and cardiovascular control \[9\]. HFD induced obesity results in alterations in circulating hormone and immune profile, which over time specifically damages lean-promoting POMC neurons. A recent publication reported damaging effects that are occur in the arcuate nucleus in mice under the HFD condition \[5\]. Based on this finding, Laing et al further demonstrated that while HFD reduced POMC-expressing neuron number in the arcuate nucleus compared to mice that were fed normal chow, the POMC-expressing neuron number was remarkably restored after voluntary exercise training. This was largely due to decreased POMC expressing neuron apoptosis, despite the fact that limited hypothalamic proliferation was observed. Consistent with this result, phosphorylation of downstream leptin signaling pathway target signal transducer and activator of transcription 3 (pSTAT3) is reduced under the HFD condition but is normalized by exercise training. Impairment of leptin signaling via Jak2-Stat3 pathway is sufficient to cause obesity \[10\], and may be related to DIO-induced activation of IKKβ/NFκβ SOCS3 regulation \[11, 12\]. The exercise-induced structural and functional neuroprotective benefits are reflective of improved input-arcuate-output coordination, resulting in a shift towards promotion of the lean phenotype by the central nervous system.

**Exercise-induced adaptation improves whole body metabolism and occurs across peripheral organs**

Sustainment of healthy body composition requires the coordination of organs of the body involved in energy homeostasis such as the adipose, liver, and skeletal muscle. The functions of these metabolic organs are tightly regulated by the central nervous system, particularly, by the neurons residing in the hypothalamus, such as POMC expressing neuron. Laing et al. showed that compared to HFD alone, the increase in the size of white adipocytes is reduced by voluntary exercise training. In the liver, steatosis and lipid droplet accumulation is increased with HFD but reduced by exercise training with HFD. In skeletal muscle, insulin signaling via phosphorylation of AKT is reduced by high-fat diet but improved by HFD with exercise. Reduced insulin signaling in skeletal muscle results in whole body reductions in impaired glucose clearance after a meal, glucose tolerance test and insulin tolerance test. Taken together, exercise-induced adaptations across organ systems result in improved whole body energy homeostasis under the chronic HFD induced obesity condition.
Conclusion

In summary, Laing et al. demonstrated that exercise exerts neuroprotective effects that occur in concert with a healthier metabolic phenotype and improved peripheral organs. The beneficial effects of exercise do not occur within any isolated organ system, but rather through the interaction of central nervous system and peripheral organs. While POMC-expressing neurons do not expend much energy relative the whole body, the effect of gain/loss of POMC neuron function on energy homeostasis via hormonal and autonomic outputs indicates that they are multi-organ coordinators. Changes in function associated with exercise under high fat diet condition in other neuronal populations, such as agouti-related peptide expressing neurons, needs to be explored further in the future. The neuroprotective benefits of exercise treatment in Laing’s study are consistent with improved coordination across organ systems to result in improved health.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Author contributions

Brenton Laing assisted to conduct the highlighted experiment and collect/analyze samples, cared for animals, and completed first and final draft of the highlight review manuscript. Hu Huang conceived highlighted experiments, provided resources, conducted data analysis, and revised manuscript.

Abbreviations

DIO: Diet-Induced Obesity; HFD: High-Fat Diet; POMC: Pro-opiomelanocortin; AgRP: Agouti-Related Peptide.

References