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The hypothalamic regulation of metabolic adaptations to exercise

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Abstract

Our modern lifestyle is characterised by easy access to nutrient dense foods combined with limited physical activity. A sedentary lifestyle is one of several factors that have contributed to the global obesity epidemic and it also predisposes to chronic illnesses such as diabetes and cardiovascular disease. Although many studies have focused on the benefits of exercise in peripheral tissues, the contributions of the central nervous system to these exercise-induced metabolic adaptations are relatively unknown. The present review highlights the role of the ventromedial hypothalamus in regulating the metabolic response to exercise.

Keywords

energy expenditure; exercise; hypothalamus; metabolism; ventromedial hypothalamus

1 | INTRODUCTION

The central nervous system (CNS) is crucial for coordinating whole body metabolism to regulate energy homeostasis.^{1,2} Currently, approximately 30% of the world population is overweight or obese,³ and the rates for obesity and associated diseases are continuing to rise. Regular exercise has been shown to be a successful lifestyle intervention⁴ by dramatically improving metabolic health (eg, increasing insulin-sensitivity and glucose disposal, increasing lean mass, reducing fat mass and increasing oxidative metabolism).^{5–10} The ventromedial nucleus of the hypothalamus (VMH) is a critical region of the CNS that regulates numerous physiological processes. In this review, we provide evidence that the VMH may be a key nucleus within the CNS to coordinate metabolic adaptations to exercise.

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2 | VMH STRUCTURE AND FUNCTIONS

The VMH is a relatively large nucleus within the hypothalamus and can be anatomically categorised into three subdivisions: dorsal medial (VMHdm), central (VMHc) and ventral lateral (VMHvl).¹¹ Each VMH-subdivision has distinct and overlapping roles in the biological regulation of behaviour, reproduction and metabolism. The VMHdm/c plays a critical role in the regulation of defensive behaviour, such as predator-responsive freezing and fleeing,^{12,13} whereas the VMHvl regulates sexual and aggressive behaviour, such as attacking or dominance over other mice.¹⁴ In addition to anatomical divisions, genes also show regional expression patterns. Genes such as vesicular glutamate transporter 2 (*Vglut2*), cerebellin 1 precursor (*Cbln1*), corticotrophin-releasing hormone receptor 2 (*Crhr2*), special AT-rich sequence-binding protein 2 (*Satb2*), ataxin 2-binding protein 1 (*Rbfox1*) and pituitary adenylate cyclase-activating polypeptide (*Pacap*) are ubiquitously expressed throughout the VMH.^{15,16} However, vestigial-like 2 homologue (*Vgll2*) is predominantly expressed in the VMHdm¹⁶; leptin receptor (*Lepr*) and neuropeptide Y (*Npy*) are localised to the VMHdm and VMHc;^{15,17,18} and oestrogen receptor- α (ER α) and NK2 homeobox 1 (Nkx2.1) expression are restricted to the VMHvl.^{15,19}

The VMH-specific orphan nuclear receptor, steroidogenic factor 1 (SF-1, official gene name *Nr5a1*),²⁰ is necessary for the proper development of the VMH cytoarchitecture and it is expressed throughout the VMH during early embryonic development.^{12,21} However, once the VMH is formed (at approximately embryonic day 17.5), the expression pattern of SF-1 begins to shift and, by post-embryonic day 0, SF-1 is restricted to the VMHdm and VMHc.^{12,15} The recent development of a SF-1 Cre-expressing mouse line²² has enabled the targeted manipulation of gene expression within the VMH and has also opened up a new era for researchers investigating VMH function.

Classical studies have shown that the VMH is key for orchestrating many aspects of metabolism, including food intake, energy expenditure, and carbohydrate and fat metabolism.²³ In 1966, Shimazu *et al.*²⁴ first demonstrated that electrostimulation of the VMH increases circulating glucose and free fatty acid (FFA) concentrations in rodents. Electrostimulation of the VMH has also been shown to increase glucagon and catecholamine levels, likely contributing to the increase of glucose and FFA.²⁵ These classic studies have recently been confirmed by studies using optogenetics, with photostimulation of SF-1 positive neurones in the VMHdm/c increasing circulating glucose, corticosterone and glucagon.²⁶

Interestingly, several of these studies suggest that the VMH may regulate metabolism in a sexually dimorphic manner. Correa *et al.*¹⁹ found that chemogenic stimulation of the VMHvl dramatically increased oxygen consumption in female mice but not in males. Furthermore, deletion of the VMHvl-specific gene Nkx2.1 led to severe obesity and reduced energy expenditure in female mice.¹⁹ These differences may be a result of sex-specific differences in the expression of ER α in the VMHvl.^{19,27} More work is needed to identify other potential sex differences resulting from VMH manipulation.

3 | THE VMH REGULATES METABOLIC ADAPTATIONS TO EXERCISE

Recent studies utilising sophisticated genetic tools show that the main role of the VMH is to regulate energy expenditure and substrate utilisation.²⁶ The VMH is required for adaptive energy expenditure in response to environmental challenges such as hypoglycaemia,^{28,29} a high-fat diet (HFD)³⁰ and ageing.^{31,32} For example, mice with gene specific manipulations in the VMH develop severe obesity and show impaired diet-induced thermogenesis only when fed a HFD.³⁰

Exercise is another metabolic challenge that disrupts homeostasis and this requires the rapid use and mobilisation of energy substrates to satisfy changing energy demands.

Exercise is a potent stimulator of sympathetic nervous system (SNS) activity and catecholamine secretion,^{33–37} increasing lipolysis, glycogenolysis and increasing blood flow to enhance nutrient delivery and waste removal.³⁸

The SNS mediates VMH-regulated peripheral glucose uptake. Microinjections of leptin or orexin into the VMH increase skeletal muscle glucose uptake and these effects are blunted by adrenergic receptors (AdR) antagonists.^{38–40} Intriguingly, β AdR 2 agonists potently increase skeletal muscle mass^{41–43} and peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α) mRNA expression.⁴⁴ Not surprisingly, moderate and high intensity exercise increases catecholamines in humans^{33,34} and rodents.^{45,46} Moreover, β AdR2 antagonists can suppress exercise-induced PGC-1 α mRNA⁴⁷ and other transcriptional signals⁴⁶ that regulate glucose, fatty acid and protein metabolism in skeletal muscle.

Scheurink *et al.*⁴⁸ previously investigated the role of the VMH in the regulation of metabolism in response to exercise. They found that administration of α - or β -AdR antagonists in the VMH of exercising rats reciprocally altered circulating glucose and fatty acids without changing insulin levels.⁴⁸ Follow-up studies found that injection of the anesthetic Marcain into the VMH during exercise impaired glucose mobilisation,⁴⁹ whereas injection of the anesthetic lidocaine inhibited fatty acid oxidation.⁵⁰ Interestingly, inhibition of VMH activity with α - and β -AdRs antagonists or lidocaine did not have an effect in sedentary animals.^{50,51} In line with these findings, stimulating the VMH in sedentary animals has repeatedly been shown to elevate circulating glucose levels and enhance glucose uptake by skeletal muscle.^{24,38,40,52} Additionally, muscarinic receptors in the VMH regulate body temperature and oxygen consumption in response to exercise.^{53,54} These studies demonstrate that VMH neurones contribute to the regulation of metabolism through the partitioning of energy substrates, energy expenditure and heat dissipation. However, questions still remain concerning which specific neuronal populations within the VMH, as well as what mechanistic signals within these neurones, are important for acute and chronic metabolic adaptations to exercise training.

Although the VMH-SNS axis is likely the key regulator of skeletal muscle adaptations to exercise, whether SF-1 neurones regulate SNS activity during/post exercise is still an open question. SF-1 neurones directly and indirectly project to neuronal sites such as the parabrachial nucleus, nucleus of the solitary tract and rostral ventrolateral medulla, which

regulate SNS activity.⁵⁵ Optogenic or chemogenic activation of SF-1 neurones alters SNS-dependent physiological responses, such as increases in heart rate¹³ and glucose levels.²⁶ We recently found that exercise training increases the mRNA levels of SF-1 and putative SF-1 target genes in the mediobasal hypothalamus (which includes the VMH).⁵⁶ Mice lacking SF-1 from the VMH had a blunted response to training-induced improvements in whole body energy expenditure, catecholamine release, fat loss and body composition. This is consistent with studies showing that the VMH modulates fatty acid mobilisation and oxidation during exercise.^{48,50} Unexpectedly, deletion of SF-1 in the VMH also impaired exercise-induced increases in skeletal muscle mass and PGC-1 α mRNA expression.⁵⁶

4 | PERIPHERAL ENERGY STATUS AND THE VMH

The mechanism by which the VMH neurones sense peripheral metabolic status during/post exercise, as well as how the VMH neurones translate these peripheral cues into metabolic adaptations, remains unclear. The VMH can sense circulating glucose levels, and the local concentration of glucose in the VMH reflects the levels of circulating glucose.⁵⁷ A microinjection of 2-deoxyglucose into the VMH can induce counter-regulatory responses to hypoglycaemia and elevate circulating glucose levels.²⁸ Additionally, microinjections of glucose into the VMH can block the response to hypoglycaemia.²⁹ Furthermore, VGLUT2 expression in SF-1 neurones is required for adaptations to hypoglycaemia.⁵⁸

Ventromedial hypothalamus neurones also appear to be activated or inhibited by other nutrients, including fatty acids,⁵⁹ ketone bodies⁶⁰ and lactate,⁶¹ all of which are increased in the post-exercise circulation. Although it is still not clear whether exercise can change local concentration of these nutrients within VMH neurones, it is reasonable to postulate that, similar to glucosensing, the VMH can detect dynamic changes of these nutrients during and after exercise.

Myokines are defined as peptides or cytokines that are released into the circulation from the skeletal muscle. Exercise has been shown to stimulate the release of myokines such as interleukin-6, which then act in other tissues such as liver, pancreas and adipose tissues to regulate metabolism.⁶² However, it is unclear whether myokines directly act on neurones within the VMH.

5 | REMARKS AND PERSPECTIVE

The VMH is a complex structure, and its role in the regulation of metabolism, especially during exercise, is not well understood. The identification of molecular markers and the development of transgenic mouse models have significantly advanced our current understanding. However, although the SF-1 Cre mouse is a useful tool for manipulating the VMH neurones, the differential expression pattern of SF-1 during development limits its usefulness. The development of inducible mouse models, such as a tamoxifen-inducible CreERT² system,^{63–66} will allow us to temporally manipulate SF-1 neurones and overcome these issues. Novel genetic and technological tools to manipulate each VMH subdivision are also needed. Unravelling the mechanisms that regulate VMH function in metabolic

adaptations to exercise (Figure 1) may lead to the development of new therapeutic resources for the treatment of obesity, diabetes and other metabolic diseases.

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FIGURE 1.

A summary of the mechanism by which the hypothalamus regulates metabolic adaptations in the peripheral tissues to exercise. FFA, free fatty acid