Published in final edited form as:

Mol Cell Endocrinol. 2011 April 10; 336(1-2): 219–223. doi:10.1016/j.mce.2010.11.019.

SF-1 in the Ventral Medial Hypothalamic Nucleus: A Key Regulator of Homeostasis

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Abstract

The ventral medial hypothalamic nucleus (VMH) regulates food intake and body weight homeostasis. The nuclear receptor NR5A1 (Steroidogenic factor 1; SF-1) is a transcription factor whose expression is highly restricted in the VMH and is required for the development of the nucleus. Neurons expressing SF-1 in the VMH have emerged as playing important roles in the regulation of body weight and energy homeostasis. Many of these studies have used site-specific gene KO approaches, providing insights into the molecular mechanisms underlying the regulation of energy homeostasis by the SF-1 neurons of the VMH. In this brief review, we will focus on recent studies defining the molecular mechanisms regulating energy homeostasis and body weight in the VMH, particularly stressing the SF-1 expressing neurons.

Keywords

ARH, arcuate nucleus of the hypothalamus; Diet-induced obesity; DMH, dorsomedial hypothalamic nucleus; Energy homeostasis; SF-1, steroidogenic factor 1; VMH, ventral medial nucleus of the hypothalamus

1. Introduction

The ventral medial nucleus of the hypothalamus (VMH) is a cell group located in the mediobasal hypothalamus, adjacent to the third ventricle and lying above the arcuate nucleus of the hypothalamus (ARH), median eminence (ME), and the pituitary gland. The cytostructure of the VMH is easily defined by the surrounding cell-poor, dendrite fiber-rich zone, which provides strong neuronal connection to the stria terminalis (Heimer and Nauta, 1969). A number of genes expressed in the VMH have been identified, and recently the function of these genes has been extensively studied. For example, Segal and colleagues used laser-capture microdissection to define VMH-enriched genes relative to the other hypothalamic regions (Segal et al., 2005). Similarly, another recent study showed ~200 genes highly enriched in neonatal (postnatal day 0) mouse VMH tissue, revealing distinct regional patterns in the newly formed VMH (Kurrasch et al., 2007).

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Although the molecular and chemical mechanisms by which the VMH is formed remain to be defined, many studies have shown that the nuclear receptor steroidogenic factor 1 (SF-1) is essential for VMH development and function (Ikeda et al., 1995; Shinoda et al., 1995; Parker et al., 2002; Zhao et al., 2008). For example, these studies demonstrated that loss of SF-1 leads to changes not only in VMH cellular topography, but also in neuronal connections of the VMH. The VMH becomes a distinct hypothalamic nuclear group around between E15 and E17 in the mouse (Tobet et al., 1999) and immunoactivity of SF-1 was detectable from mouse diencephalons as early as E9.5 days (Ikeda et al., 2001). The VMH has long been considered a hypothalamic nucleus responsible for regulation of food intake and body weight homeostasis (Hetherington and Ranson, 1940; Elmquist et al., 1999; Broberger and Hokfelt, 2001). In addition, several groups, starting in the 1960s, suggested that the VMH lesions mainly affect sympathetic nervous system resulting in reduction of sympathetic tone, increase of fat mass, and induction of hyperinsulinemia (Bernardis and Frohman, 1971; Cox and Powley, 1981; Nijima et al., 1984). These lesion studies may have resulted in impaired energy homeostasis due to concomitant lesions on the ARH or the proopiomelanocortin (POMC) neurons of the ARH (Saper et al., 2002). However, several studies support the notion that the VMH plays an important role in regulation of energy homeostasis by regulating autonomic nervous system activity; the molecular mechanisms underlying these responses remained unclear.

A key finding in this regard was made by Keith Parker and colleagues who found that SF-1, a nuclear receptor expressed only in the VMH of the brain, is required for VMH development and normal regulation of energy balance (Majdic et al., 2002). Briefly, they created viable SF-1 KO mice by performing syngeneic adrenal transplants between littermates with supplementary glucocorticoid injections. This was key since global SF-1 deletion is lethal due to adrenal agenesis. The “rescued” SF-1 KO mice developed severe obesity due mainly to decreased activity. This approach however was confounded by the potential secondary metabolic effects from glucocorticoid injections and adrenal transplantations. Nonetheless, this report provided genetic evidence that the VMH (specifically SF-1 neurons) plays important roles in the regulation of energy balance. Since this report from the Parker group, many laboratories have investigated the roles of SF-1 neurons in the regulation of energy homeostasis and metabolism.

2. Development of SF-1 Cre Lines

To understand the molecular mechanisms underlying the body-weight homeostasis regulated by SF-1 neurons of the VMH, two independent groups developed specific Cre lines mediated by SF-1 regulatory elements (Bingham et al., 2006; Dhillon et al., 2006). Although both of them used a bacterial artificial chromosome (BAC) containing the SF-1 gene, the two SF-1 Cre transgenes were slightly different in terms of insertion site for Cre recombinase and the length of BAC used. For example, Bingham et al., inserted the Cre construct in between exon 2 located 22kb from the 5'-flanking region and 88kb from the 3'-flanking region (Bingham et al., 2006). Dhillon and colleagues flanked the construct of Cre recombinase between exon 2 and exon 4 ranging ~32kb on the 5' region and ~106kb on its 3' end. Both Cre lines showed expression of Cre recombinase in the pituitary gland, adrenal glands, and the gonads where endogenous SF-1 is expressed. Importantly, the Cre activity also was detected in the SF-1 neurons of the VMH in the brain, providing a tool to dissect specific molecular mechanisms in the SF-1 neurons.

3. Direct Leptin Action in SF-1 Neurons

Mice lacking leptin (*ob/ob*) and the leptin receptor (*db/db*) are massively obese, hyperphagic, and display complex metabolic abnormalities including hepatic steatosis, and

impaired thermoregulation, and glucose metabolism (Loten et al., 1974; Campfield, 2000). Additionally, *ob/ob* mice develop obesity with increased fat mass when pair-fed. These results demonstrate that decreased energy expenditure and hyperphagia both contribute to the severe obesity seen in leptin-deficient mice. It is established that the brain plays essential roles mediating the effects of leptin. This has been demonstrated by several studies including those with central nervous system-specific leptin receptor (LepR) KO and transgenic mice in which the LepR was specifically removed or reconstituted in specific regions of the brain (Cohen et al., 2001; de Luca et al., 2005). In addition, several hypothalamic nuclei including the arcuate nucleus of the hypothalamus (ARH), the ventral medial hypothalamus (VMH), the dorsomedial nucleus of the hypothalamus (DMH), and the lateral hypothalamus (Legenbauer et al.) abundantly express LepR (Mercer et al., 1996; Elmquist et al., 1997; Elmquist et al., 1998; Scott et al., 2009). This broad expression of the LepR within the hypothalamus suggests that the effects of leptin might not be restricted to one site in the brain, and therefore identifying specific brain sites mediating leptin action are needed to be experimentally addressed. This included the potential action of leptin on SF-1 neurons in the VMH.

The role of leptin in SF-1 neurons was addressed independently by two groups using the SF-1 Cre lines described above. Both groups generated mice lacking LepRs in SF-1 neurons (Dhillon et al., 2006; Bingham et al., 2008) and found that the mice were obese, especially following a high fat diet. This included increased adiposity and body weight. The Lowell and Elmquist group observed mild obesity in mice fed a chow diet; however, the Parker group did not detect a difference in body weight.

Notably, the KO mice lacking LepR in SF-1 neurons showed significant body weight gain displaying comparable magnitude with *Pomc* neuron-specific LepR KO mice (Figure 1A and 1B). An additive effect on body weight was exhibited when the LepR was deleted in both *Pomc* and SF-1 neurons, further indicating that LepRs in SF-1 neurons are required for normal body weight homeostasis (Balthasar et al., 2004) (Figure 1A and 1B). Interestingly, the SF-1 neuron-specific LepR KO mice were more sensitive to high fat diet, showing blunted suppression in food intake and impaired energy expenditure compared to WT controls (Dhillon et al., 2006; Bingham et al., 2008). These results suggest that leptin and leptin receptor signaling may play an important role in resistance to diet-induced obesity. Also, these studies demonstrate that the SF-1 neurons in the VMH are direct targets of leptin required for mediating appropriate energy balance, especially in the face of a high caloric environment.

Following the aforementioned studies, Flier and colleagues deleted a negative regulator of leptin signaling in SF-1 neurons. Specifically, they deleted suppressor of cytokine signaling 3 (*Socs3*), a negative regulator of leptin receptor signaling and a potential mediator of central leptin resistance, in the SF-1 neurons of the VMH (Zhang et al., 2008). They reported that the mice lacking *Socs3* in the SF-1 cells demonstrated enhanced sensitivity to exogenous leptin. In addition, the KO mice exhibited increased glucose sensitivity and food intake reduction. However, they did not detect differences in body weight between genotypes. They did report an unexpected decrease of energy expenditure in *Socs3* KO animals. Based on this result, they suggested that the decreased energy expenditure might be a factor associated with comparable body weight between WT and *Socs3* KO in SF-1 neurons. Collectively, these results suggest that leptin action in SF-1 neurons is important in the regulation of energy balance and energy expenditure.

Several reports have suggested that leptin mediates some of its effects via activation of phosphatidylinositol 3-kinase (PI3K) signaling in the hypothalamus (Niswender et al., 2001; Zhao et al., 2002; Morton et al., 2005). Several groups have recently investigated the

role of PI3K signaling in POMC and Agrp neurons in the arcuate nucleus of the hypothalamus; their role in VMH neurons was not assessed (Hill et al., 2008; Al-Qassab et al., 2009). Therefore, we recently disrupted PI3K signaling in SF-1 neurons. Specifically, we deleted the PI3K catalytic subunit p110 α , in SF-1 neurons of the VMH (Xu et al., 2010). Briefly, we found that chow-fed male mice lacking PI3K (*p110 α ^{lox/lox}/SF1-Cre*) in SF-1 neurons showed comparable body weight and body composition as their littermates (*p110 α ^{lox/lox}*) (Figure 2A and B). However, male *p110 α ^{lox/lox}/SF1-Cre* mice exhibited increased susceptibility to high fat diet, displaying significantly increased body weight and adiposity compared to their controls (Figure 2C and D). Notably, these observations are consistent with previous VMH ablation studies in which lesioned animals displayed increased sensitivity to diet-induced obesity (Inoue et al., 1977; Rohner-Jeanrenaud et al., 1982; Nijima et al., 1984; Oku et al., 1984). Taken together, these findings suggest that PI3K signaling in SF-1 neurons is required for appropriate responses to excess calories and this may be key in the development of diet-induced obesity.

To assess potential mechanisms underlying the increased sensitivity to high fat diet in *p110 α ^{lox/lox}/SF1-Cre* mice, we performed indirect calorimetry studies. The *p110 α ^{lox/lox}/SF1-Cre* mice consumed comparable amounts of food with their littermate counterparts on either normal chow or high fat diet (Figure 3A and B). In addition, no significant difference in energy expenditure was detected between *p110 α ^{lox/lox}/SF1-Cre* and their controls in normal chow condition. However, we found significantly reduced energy expenditure (i.e. O₂ consumption, CO₂ production, and heat production) in high fat fed *p110 α ^{lox/lox}/SF1-Cre* mice (Figure 3C-E). To test whether the reduced energy expenditure was due mainly to maladaptation to excess nutrition and impaired diet-induced thermogenesis, we acutely exposed weight-matched *p110 α ^{lox/lox}/SF1-Cre* and their littermates the mice to HFD. Expectedly (Lowell and Spiegelman, 2000), the *p110 α ^{lox/lox}/SF1-Cre* and control mice exhibited increased O₂ consumption, CO₂ production, and heat production. However, this acute increase in energy expenditure was significantly blunted in the *p110 α ^{lox/lox}/SF1-Cre* mice compared to their controls (Figure 4A-C). This impaired thermogenic responses to acute HFD in *p110 α ^{lox/lox}/SF1-Cre* mice was not due to reduction in energy intake, as food intake was comparable between genotypes (Xu et al., 2010). These results suggest that the PI3K signaling in SF-1 neurons play important roles in resisting diet induced obesity by regulating diet-induced thermogenesis.

4. Concluding Remarks

Recently, details of the neurocircuitry regulating energy balance have been identified. However, the underlying molecular and chemical mechanisms in these brain sites are still not well established. Since the classic lesion studies of Hetherington and Ranson (Hetherington and Ranson, 1940), the VMH has been considered as a critical hypothalamic nucleus regulating energy homeostasis. These earlier studies were based on physical or chemical lesions or electrical stimulation in the VMH. However, due to the pioneering work of Keith Parker and his colleagues it has become clear that SF-1 neurons in the VMH are key regulators of energy balance. Recent studies have extended this line of investigation and have supported key roles of SF-1 neurons in regulating energy expenditure in the context of high fat diet feeding. Collectively, these studies have provided important new insights into the molecular mechanisms underlying the regulation of energy homeostasis by the SF-1 neurons of the VMH. Moving forward, an increased understanding of the gene expression programs regulated by SF-1 may prove invaluable mechanisms in the face of increasing rates of obesity.

Acknowledgments

We thank Dr. Yun-Hee Choi and Anne Reuter (UT Southwestern Medical Center) for helpful discussions and suggestions. We also thank UTSW Mouse Metabolic Phenotyping Core (supported by PL1 DK081182 and UL1RR024923). This study was supported by National Institutes of Health Grants RL1DK081185 (to J.K.E.).

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Figure 1. Effect of SF-1 neuron-specific Deletion of LepR on Body Weight
 (A) Body weight from male mice. (B) Body weight from female mice. Graphs are represented as mean $\pm$ SEM. N=10-12 per group. This figure excerpted from Dhillon *et al.*, 2006.

Figure 2. Deletion of PI3K (p110 α) in SF-1 Neurons of the VMH Increases Sensitivity to Diet-Induced Obesity

(A) Weekly body weight was measured in group-housed male mice fed normal chow (n=12/group).

(B) Body composition of male mice aged 15 weeks old fed normal chow (n=12/group).

(C) Weekly body weight was measured in group-housed male mice fed high fat diet (n=16 or 23/genotype).

(D) Body composition of male mice aged 18 weeks old fed high fat diet (n=10/genotype).

Data are expressed as mean $\pm$ SEM (*P<0.05 and **P<0.01, student's t-test). Reprinted from Xu *et al.*, 2010.

Figure 3. Deletion of p110 α in SF-1 Neurons Reduces Energy Expenditure

(A and B) Daily food intake was measured in 7-week-old male mice with comparable body weight fed with regular chow (A) or with high fat diet (B) (n=11-15/genotype).

(C-E) Seven-week-old chow-fed-male mice (n=11 or 16/genotype) were fed with high fat diet for 2 weeks and matched body weight ($p110\alpha^{lox/lox}$: 23.8 ± 0.7 g versus $p110\alpha^{lox/lox}/SF1-Cre$: 24.9 ± 0.7 g, $p=0.31$), followed by metabolic analyses using the TSE system. Graphs are represented as mean $\pm$ SEM (* $P < 0.05$ and ** $P < 0.01$, t-test). Data were originally published in Xu *et al.*, 2010.

Figure 4. Impaired Thermogenic Regulation in SF-1 neuron-specific *p110α* KO mice in Response to High Fat Diet Feeding

(A-C) Six-month-old chow-fed male mice (n=6/genotype) were matched for body weight (*p110α^{lox/lox}*: 37.7±1.4g versus *p110α^{lox/lox}/SF1-Cre*: 37.4±1.0g, p=0.9) and adapted to the TSE chambers. The mice were provided with HFD at 17:00 (2hr prior to dark cycle), and metabolic parameters were monitored from 24 hr before the high fat diet feeding until 24 hr after using the TSE metabolic chambers. (Top) Temporal levels of O₂ consumption (A), CO₂ production (B), and heat production (C). The arrow indicates the beginning of high fat diet feeding. (Bottom) Changes in O₂ consumption (A), CO₂ production (B), and heat production (C) between the 12hr dark cycle before high fat diet feeding and the 12 hr dark cycle after in *p110α^{lox/lox}* and *p110α^{lox/lox}/SF1-Cre* mice. The data were expressed as either average (top) or mean±SEM (*P<0.05 and **P<0.01, Student's t-test). Reprinted from Xu *et al.*, 2010.