HHS Public Access

Author manuscript

Curr Opin Endocr Metab Res. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

Curr Opin Endocr Metab Res. 2020 October ; 14: 65–72. doi:10.1016/j.coemr.2020.06.001.

Sirtuin (SIRT)-1: At the crossroads of puberty and metabolism

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Abstract

In the arcuate nucleus (ARC) of the hypothalamus reside two neuronal systems in charge of regulating feeding control and reproductive development. The melanocortin system responds to metabolic fluctuations adjusting food intake, whereas kisspeptin neurons are in charge of the excitatory control of Gonadotropin Hormone Releasing Hormone (GnRH) neurons. While it is known that the melanocortin system regulates GnRH neuronal activity, it was recently demonstrated that kisspeptin neurons not only innervate melanocortin neurons, but also play an active role in the control of metabolism. These two neuronal systems are intricately interconnected forming loops of stimulation and inhibition according to metabolic status. Furthermore, intracellular and epigenetic pathways respond to external environmental signals by changing DNA conformation and gene expression. Here we review the role of Silent mating type Information Regulation 2 homologue 1 (Sirt1), a class III NAD+ dependent protein deacetylase, in the ARC control of pubertal development and feeding behavior.

Keywords

GnRH; kisspeptin; melanocortin; arcuate nucleus; puberty; chromatin modifications; transcriptional repression; transcriptional activation; Polycomb group; Trithorax complex

Hypothalamic reproductive circuits: the role of Kisspeptin neurons

Reproductive pubertal maturation depends on the timely increase in pulsatile gonadotropin-releasing hormone (GnRH) secretion from hypothalamic GnRH neurons into the median eminence of the hypothalamus. Changes in GnRH secretion result from alterations in trans-synaptic and glial excitatory and inhibitory inputs to the GnRH neuronal network (1). During infancy, the low secretory activity of GnRH neurons results from a predominant trans-synaptic inhibitory control. At puberty, inhibitory inputs are reduced while excitatory

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Author Contributions

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Conflict of interest statement

The authors have no conflicts of interest to declare

inputs to the GnRH network increase, facilitating the pubertal transition by increasing GnRH pulsatile secretion (2,3). Increased GnRH enhances pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from pituitary gonadotropes (3). The afferent control of GnRH neurons is determined by trans-synaptic inputs from hypothalamic nuclei including the anteroventral periventricular nucleus (AVPV), arcuate nucleus (ARC) and median eminence (ME), mediated by neuropeptides (Kisspeptins, Neurokinin B, GnIH, etc), neurotransmitters (Glutamate, GABA, etc), glial factors (EGF family growth factors and prostaglandins) and other molecules like estrogen (E2), nitric oxide and leptin, among others (4,5).

In rodents, kisspeptin neurons are the main stimulators of GnRH release and are located in both the ARC and the anteroventral periventricular (AVPV) nucleus. These neurons release the kisspeptin peptides that stimulate GnRH release by binding its G-protein coupled receptor KISS1R/GPR54 expressed in GnRH neurons. These two populations of kisspeptin neurons are differentially regulated in a sex and estrogen-dependent manner (6). Kisspeptin neurons from the ARC, that also express neurokinin B (NKB) and Dynorphin A, two neuropeptides that stimulate and inhibit kisspeptin secretion respectively (7), are involved in the pulsatile release of GnRH. Kispeptin neurons from the AVPV are involved in the E2 induced LH surge that leads to ovulation (6).

During pubertal maturation, increased ARC kisspeptin expression is needed for the “reawakening” of the GnRH pulse generator. Later on, during low or depleted plasma E2 levels (like the ones seeing during the diestrus phase), ARC *Kiss1* mRNA expression is enhanced, increasing the pulsatile release of GnRH, ultimately inducing gonadotropin release from the pituitary gland. On the other hand, increased E2 in bloodstream (like the one seeing during the proestrus phase) activates *Kiss1* mRNA expression in the AVPV, contributing with the surge of LH that leads to ovulation (8).

Reproduction is a metabolically demanding process highly coordinated by the nutritional status of the individual. Under periods of insufficient energy balance, hypothalamic neuronal circuits boost food consumption and prevent energy-demanding processes like pregnancy (9,10). The ARC integrates internal neuronal signals with hormonal status and external nutrient availability (11–13), making the hypothalamus a key primary regulator of reproduction and energy homeostasis (11–14).

The Arcuate Nucleus of the hypothalamus: a hub for metabolic and reproductive signals

The ARC is home for the central melanocortin system (15–18), a neuronal pathway that acts like a rheostat of energy availability. While pro-opiomelanocortin / cocaine amphetamine-related transcript (POMC/CART) neurons are involved in transmitting satiety signals under conditions of energy excess, neuropeptide Y / agouti related neuropeptide (NPY/AgRP) neurons are responsible for food seeking behavior under conditions of energy deprivation (13,16,17,19,20).

In this same region resides the population of Kiss1/Kisspeptin neurons largely responsible for the pulsatile control of gonadotropin hormone (GnRH) and the timely initiation of puberty and adult fertility (21–24). Moreover, several studies point to the role of ARC *Kiss1* neurons as central integrators of energy balance regulation of reproduction (25–28). Furthermore, since the median eminence (ME) is devoid of the typical blood-brain barrier, the ARC integrates circulating hormonal and metabolic signals that impact both the melanocortin system and *Kiss1* neurons as well (29–31).

Conditions of negative energy balance, diminish hypothalamic *Kiss1* expression and delay pubertal development (32,33), while energy excess during early development increases hypothalamic *Kiss1* and advances puberty (34). When energy excess is presented persistently during adulthood, hypothalamic *Kiss1* expression is reduced (35,36), a condition usually associated with hypogonadotropic hypogonadism. While some of the metabolic effects on the neuroendocrine reproductive system seem to be directly associated with the Kisspeptin system (33,34,37), there is compelling evidence of an indirect action of key metabolic mediators, like leptin and insulin, on upstream pathways involved in energy homeostasis like the melanocortin system (38,39).

Leptin, a hormone produced by fat cells and in charge of transmitting satiety signals to the brain, controls POMC gene expression trough leptin receptor (OB-Rb) mediated activation of signal transducer and activator transcription factor (STAT3), which binds to Specificity Protein 1 (SP1) at POMC promoter regions (40,41). Ob-Rb is widely expressed in the hypothalamus and its early absence in life has been associated with delayed puberty, reduced GnRH release and low circulating gonadotropin levels (39). Leptin also stimulates alpha-Melanocyte stimulating hormone (α-MSH) released from POMC neurons that ultimately increases GnRH/LH release (42). This stimulatory action is mediated by α-MSH receptors MC3R and MC4R, since double knockout animals are the only ones showing impaired reproduction (43). While the reproductive actions of ARC α-MSH are in part directly mediated by MC3R and MC4R in GnRH neurons (44,45), it has been shown that POMC neurons are in close apposition with ARC *Kiss1* cell bodies, possibly transmitting some of the metabolic signals from the melanocortin system (44). Moreover, it was recently shown that ARC *Kiss1* neurons induce POMC neuron depolarization via glutamate metabotropic receptors (46), attesting to the high interplay between the central reproductive network and the melanocortin system.

ARC NPY/AgRP neurons respond to conditions of negative energy balance (like fasting) and operate as endogenous antagonists of MC3/4R (47,48). AgRP increases feeding behavior by blocking α-MSH signaling from POMC neurons and by increasing GABAergic neurotransmission (49,50). Leptin deficiency enhances NPY and AgRP expression in the ARC and produces infertility in mice reversible by AgRP and NPY receptor ablation (51–53). Although some contradictory findings have been reported, the overall function of NPY/AgRP neurons is to restrain the reproductive axis by suppressing GnRH/LH secretion (54–60).

Recent reports demonstrate the NPY/AgRP neurons innervate hypothalamic *Kiss1* neurons and that optogenetic stimulation of AgRP cells, affects estrous cyclicity trough increased

GABAergic tone to *Kiss1* neurons, similar to conditions of negative energy balance (28,61). Moreover, *Kiss1* neurons stimulate NPY/AgRP neurons via glutamate metabotropic receptors (46). Additionally, Kiss1r/GPR54 KO mice show increased adiposity and body weight (62), and decreased energy expenditure after 8 to 9 weeks of life, a phenotype more evident in females (63,64). Despite increased adiposity, Kiss1r KO mice showed reduced food intake with no change in melanocortin gene expression (64). This could be due to disrupted circadian feeding behavior (65) or decrease energy expenditure trough kisspeptin mediated altered function of the paraventricular nucleus (PVN), the bed nucleus of the stria terminalis or the lateral hypothalamus (LH) (66,67).

The aforementioned scientific evidence underlies the intricate relationship between the melanocortin system and the kisspeptin control of reproduction. These systems are the control center of appetite and reproduction respectively, in charge of integrating the peripheral metabolic signals (Leptin and insulin) with the appropriate neuro-physiological responses.

ARC epigenetic mechanisms regulating reproductive circuits and food intake.

During the last several years we have demonstrated that there is an epigenetic layer of regulation that controls the developmental process by which GnRH release is kept in check during infancy, and also during the increase in GnRH secretion that brings about the pubertal process (68–70). A central target of this epigenetic mode of control is the transcriptional machinery of ARC Kisspeptin neurons that facilitate GnRH release during the pubertal transition. A set of transcriptional regulators with epigenetic capabilities are involved in the transcriptional control of the *Kiss1* gene. During the infantile period, the Polycomb Group (PcG) of transcriptional repressors keep *Kiss1* gene expression low by increased chromatin compaction at the *Kiss1* locus due to enhanced trimethylation of Histone 3 at lysine 27 (H3K27me3) (68). During this same period, there is low levels of the activating histone modification H3K4me2/3 due to the enhanced activity of the histone demethylase KDM1A targeted to the *Kiss1* and *Tac3* loci by GATAD1 (70). At the pubertal transition, the chromatin landscape changes at both the *Kiss1* and the *Tac3* loci, by removal of the PcG and GATAD1/KDM1A repressors, in favor of MLL1 and MLL3, two members of the Trithorax Group (TrxG) of transcriptional activators. The TrxG activates *Kiss1/Tac3* gene expression by decreasing chromatin compaction due to enhanced H3K4me3 at their promoter region and by recruiting p300/CBP acetyltransferases at distal enhancer sites (69).

Obesity can be associated with fetal and early postnatal life perturbations in both endocrine and metabolic pathways that may result in adverse effects during childhood and adulthood (71,72). It has been reported that cytosine-guanine (CpG) site methylation of the intron2-exon3 boundary of the *POMC* gene is hypermethylated in obese children (73), indicating a possible link between obesity of central origin and the epigenetic machinery. Maternal high fat diet (HFD) drives to obesity, hyperlipidemia, hyperinsulinemia, insulin resistance and altered glucose homeostasis in both gender offspring, with alterations in electrophysiological responses as well as hypothalamic neuropeptide expression caused by epigenetic alterations

acquired during perinatal life (74,75). HFD feeding during gestation reduces *Pomc* gene expression due to hypermethylation of the gene promoter and enhancer regions, but only promoter hypermethylation remains persisted at adulthood (76). Specifically, hypermethylation occurs at an SP1 site, preventing the transcriptional activation of *Pomc* induced by leptin, resulting in leptin resistance, increased food intake and weight gain (76). On the other hand, ARC *Pomc* promoter methylation is decreased in rats resistant to diet-induced obesity (77). Moreover, specific deletion of methyl-CpG- binding protein (MeCP2) from *Pomc* neurons results in increased food intake, obesity and leptin resistance in mice (78).

Early developmental disruption of the melanocortin system can also be due to exposure to environmental factors such as synthetic chemicals. For instance, prenatal exposure to butyl paraben (BuP) induces increased food intake and weight gain in female rodent offspring (79). BuP diminishes hypothalamic *Pomc* gene expression by increasing DNA methylation at its 5' regulatory region. This favors inappropriate control via alpha-MSH signaling to MCR4, promoting weight gain (79).

Hypothalamic neural circuits are established early in life (80,81). This period is a critical time for metabolic programming, and therefore maternal nutritional status during gestation and lactation may determine the onset of metabolic syndrome or reproductive disease in offspring (75). The role of epigenetics in the control of pubertal maturation under conditions of metabolic stress is still not completely uncovered. The alteration of hypothalamic developmental trajectories due to nutritional re-programing could be the result of microstructural reorganization of neurons and/or alteration of the hypothalamic epigenome, resulting in disrupted release of neuropeptides and receptor expression (77,82,83). Overall, these studies emphasize the central role of DNA methylation and chromatin modifications in the ARC-mediated regulation of reproductive development and metabolism.

SIRT1: a rheostat of the ARC metabolic status

The activity of most enzymes with epigenetic capabilities is dependent of cellular metabolites. Epigenetic modification of DNA at CpGs by DNA methyl-transferases (DNMTs) requires the precursor S-adenosylmethionine (SAM) from the one-carbon metabolism (84). Fluctuations in cellular methionine influence DNA methylation and gene expression. Methionine supplementation increases promoter methylation and decreases gene expression (i.e. *Reln, Bdnf*) (84).

Acetyl-CoA, produced from the catabolism of fatty acids and glucose, is the primary donor of acetyl groups in cellular histone acetylation by histone acetyl transferases (HATs), connecting energy metabolism with epigenetic reactions (85). Moreover, sirtuin-dependent histone deacetylation uses nicotinamide adenine dinucleotide (NAD+), a cofactor synthesized de novo from the amino acid tryptophan. Fluctuations in cellular NAD+ could be associated with altered gene expression induced by SIRT1-dependent histone acetylation changes (86).

SIRT1 is a class III NAD+ dependent protein deacetylase sensitive to NAD+/NADH ratio. High levels of SIRT1 expression have been detected in the brain and especially the hypothalamus (86,87). In the ARC, SIRT1 functions as a metabolic sensor, as *Pomc* neuron specific *Sirt1* knock-out mice show decreased energy expenditure and hypersensitivity to a high-fat diet (88), while SIRT1 deficiency in AgRP neurons reduces food intake (89,90). Via deacetylation of Forkhead box protein O1 (FoxO1), SIRT1 increases AgRP transcription while decreases POMC (89,91,92). In fasting animals, SIRT1 is elevated in neurons of the melanocortin system, promoting positive energy balance by increased feeding behavior. Surprisingly, diet induced obese (DIO) animals also display enhanced ARC SIRT1 (91). Inhibiting SIRT1 in DIO animals, increased POMC and α-MSH which in turn lead to augmented thyrotropin-releasing hormone (TRH), circulating T3 and increased energy expenditure (91). These results suggest that the regulation of *Pomc* neurons by SIRT1 is dependent on nutritional status.

It was recently shown that SIRT1 mediates the reduction in *Pomc* expression in the ARC induced by melanin-concentrating hormone (MCH), since *Pomc*-specific SIRT1 *knock-out* mice are resilient to MCH anorexic treatment (93). Moreover, animals overexpressing SIRT1 fed a high fat diet (HFD) did not respond to central MCH knockdown with hypophagia and weight loss (93). Although the central metabolic effects of SIRT1 in *Pomc* neurons are mediated trough deacetylation of forkhead box protein O1 (FoxO1) (93), no information is yet available on the putative role of SIRT1 as a histone modifier in the control of the melanocortin system.

Recent evidence from our laboratory and others shows a central role of neuronal and glial SIRT1 in the metabolic control of pubertal development (87,94). While it is known that SIRT1 absence in GnRH neurons induce failure in neuronal migration during early development (95), developed GnRH neurons appear to be unreceptive to metabolic signals (33). In the reproductive hypothalamus, ARC *Kiss1* neurons are probably the main integrators of nutritional cues to the GnRH network, controlling pubertal development and reproductive success. Animals grown under conditions of nutritional excess, showed a reduction in SIRT1 expression in ARC *Kiss1* neurons, increased *Kiss1* expression and advanced pubertal development, the opposite is true in underfed animals (87). ARC SIRT1 directly modifies the epigenetic landscape of the *Kiss1* gene 5'-regulatory region. During the pubertal transition, the reduction of SIRT1 expression is accompanied with increased acetylated histone 3 at lysine 9 and 14 (H3K9/14ac) at the *Kiss1* promoter, favoring a state of open chromatin conformation. Nutritional excess enhances, while undernutrition reduced this effect (87). Moreover, we demonstrated that SIRT1 physically interacts with the PcG repressor complex, increasing the repressive H3K27me3 at the *Kiss1* promoter during infanc; nutritional excess diminished, while undernutrition enhanced this association (87). Overall, these data demonstrate that ARC *Kiss1* neurons respond to metabolic challenges with changes in SIRT1 expression and association to the *Kiss1* gene promoter, affecting the chromatin landscape of the *Kiss1* gene and modulating reproductive development.

Glial SIRT1 also plays a role in glucose metabolism and reproduction (94). Overexpression of SIRT1 in astrocytes increases food intake, body weight gain and glucose intolerance. While the opposite happens in animals expressing a deacetylase-deficient (MUT) SIRT1

mutant (94). Overexpression of wild type (WT) SIRT1 in astrocytes increases the number of estrous cycles observed during a six-week period, while overexpression of the MUT SIRT1 impairs estrous cyclicity. While pituitary function was intact in WT and MUT SIRT1 overexpressing animals, hypothalamic neuropeptides seem to be altered. *Kiss1* expression was increased in WT SIRT1 overexpressing animals while *Npvf* (a repressor of GnRH release) was increased (94). We don't know what subpopulation of Kisspeptin neurons was affected in these animals, since the authors determined gene expression using the whole brain (94).

The aforementioned results show an orchestrated role of SIRT1 as integrator of metabolic signals in ARC neurons. While all the studies on the role of ARC SIRT1 in metabolic and feeding control where done in adult animals and mostly in males, we studied SIRT1 action on Kisspeptin neurons during growth and female pubertal development. In the melanocortin system, SIRT1 acts indirectly on gene expression by deacetylating FoxO1. In Kisspeptin neurons, SIRT1 acts directly on the *Kiss1* promoter region deacetylating histone marks and recruiting PcG repressors. It is also possible that ARC SIRT1 function differs before and after puberty when estrogen levels increase, since it was found that SIRT1 contributes to estrogen dependent breast cancer progression (96).

During embryogenesis, SIRT1 is involved in cortical neuronal cell fate by repressing the Wnt/Notch/Fgf/Shh pathway (97). During postnatal life, SIRT1 controls axonal growth in a model of diabetic neuropathy by deacetylating NEDD4–1 (98) and regulates dorsal root ganglion axon regeneration trough a repressive loop with microRNA-138 (miR-138) (99). Rats bred to develop diet induced obesity show a permanent reduction in leptin induced trophic action on ARC neurons (100). Moreover, in a model of delayed female puberty due to neonatal undernourishment, it was demonstrated that ARC kisspeptin fiber projections to the preoptic region are reduced (101). In view of this, it is possible that during prenatal life, SIRT1 serves as a master regulator of Kiss1, POMC and NPY neuronal cell fate, and during early postnatal life, affecting kisspeptin and melanocortin neuronal growth. Furthermore, using a model of GnRH-neuron specific Dicer knock-out, it has been shown that the increase in GnRH during the infantile to juvenile transition is dependent on the integrity of miR-200 and mir-155 (102). Interference with this system produces hypogonadotropic hypogonadism and infertility in mice (102). Similarly, loss of Dicer in POMC neurons, causes a decline in POMC expressing neurons and increase Pomc progenitors differentiating into NPY neurons in a miR-103/107 dependent manner (103). Since it is known that several microRNAs (miRNAs) target Sirt1 expression in a wide range of developmental and pathological processes (104–106), and that SIRT1 inhibits miR-138 (99), it is possible to speculate that miRNAs are involved in SIRT1 dependent GnRH expression or ARC melanocortin neuron development.

Conclusion and future directions

We focused our review in ARC networks that control appetite and reproduction. While these networks are indeed intricately interconnected, producing neuronal loops of regulation; we propose that at the cellular level, intracellular molecules integrate metabolite status information with cellular function and the epigenetic control of gene expression. Over the

last few years it has become clear that one of these molecules is SIRT1. Although SIRT1 seems to be widely expressed throughout the hypothalamus, whether in glial cells, the kisspeptin or the melanocortin neuronal network, the role of this enzyme appears to be as an intermediary between cellular metabolism and downstream gene effectors. Overfeeding can alter hypothalamic circuity, and the above-mentioned findings underscore the importance of epigenetic mechanisms and especially the role of SIRT1 in this process. It is still important to identify specifically how fluctuations in cellular metabolites (i.e. SAM, Acetyl-CoA and NAD+/NADH) affect the activity of DNA and histone methyltransferases, histone acetyltransferases and deacetylases in specific ARC populations like *Kiss1*, *Pomc* and *Agrp* neurons. Although still in its infancy, single cell genomic approaches seem to be the tools needed to identify mRNA expression and epigenetic changes in complex neuronal populations such as the ones of the ARC. Recent single cell RNA-sequencing (scRNA-seq) analysis of the adult ARC identified 24 different neuronal types, including six types of dopaminergic neurons, two types of AgRP neurons and three types of Pomc neurons (107). While single cell level identification of histone modification changes is not feasible yet, it has become clear that the study of chromatin accessibility by ATAC-seq (assay for transposition of accessible chromatin) is a reliable tool to identify chromatin transitions in isolated single cells (108). These new technologies can be used to understand the dynamism of gene/environment interactions and to help develop new potential therapies to treat pubertal disorders of central origin and obesity.

Acknowledgments

Funding sources

National Institute of Health (1R01HD084542) to A.L. and 8P51OD011092 for the operation of the Oregon National Primate Research Center.

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