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Chemical Identity of Hypothalamic Neurons Engaged by Leptin in Reproductive Control

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Abstract

The adipocyte-derived hormone leptin plays a critical role as a metabolic cue for the reproductive system. Conditions of low leptin levels observed in negative energy balance and loss-of-function mutations of leptin or leptin receptor genes are characterized by decreased fertility. In recent years, advances have been made identifying possible hypothalamic neurons relaying leptin's neuroendocrine control of reproductive function. Studies from different laboratories have demonstrated that leptin action in the hypothalamo-pituitary-gonadal (HPG) axis is exerted via hypothalamic interneurons regulating gonadotropin-releasing hormone (GnRH) cells, oppose to direct action on GnRH neurons. Following this observation, studies focused on identifying leptin responsive interneurons. Using a Cre-loxP system to re-express or delete the leptin receptor long form (LepRb) from Kisspeptin neurons, our laboratory found that leptin's action on Kiss1 cells is neither required nor sufficient for leptin's role in reproductive function. Endogenous re-expression of LepRb however, in glutamatergic neurons of the ventral premammilary nucleus (PMV) or ablation of agouti-related protein (AgRP) neurons from leptin signaling-deficient mice are both sufficient to induce puberty and improve fertility. Recent studies have also shown that leptin action in first order GABAergic neurons is required for fertility. Together, these studies begin to delineate key neuronal populations involved in leptin's action in reproduction. In this review, we discuss recent advances made in the field and highlight the questions yet to be answered.

Keywords

metabolism; glutamate; nitric oxide; GABA; melanocortin; kisspeptin

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1. Introduction

The adipocyte-derived hormone leptin, encoded by the *Lep/LEP* gene, circulates in plasma in free and bound forms (Zhang et al., 1994, Ahima and Flier, 2000, Elias and Purohit, 2013). Leptin levels in plasma are proportional to adipose tissue mass and therefore changing levels of leptin signal energy (in)sufficiency and function as a metabolic cue to allow adaptive physiologic responses (Maffei et al., 1995, Considine et al., 1996, Flier, 1998, Casanueva and Dieguez, 1999, Ahima et al., 2000, Chan and Mantzoros, 2005).

Reproductive function is energetically demanding due to the high energetic costs of pregnancy, lactation, and male territoriality (Schneider, 2004, Hill et al., 2008, Roa et al., 2010). States of negative energy balance has a negative impact in the reproductive physiology. Rodents and primates in negative energy balance show decreased sex steroids, pulsatile luteinizing hormone (LH) secretion and fertility (Manning and Bronson, 1989, Cagampang et al., 1990, Cameron and Nosbisch, 1991, Parfitt et al., 1991, Maffei et al., 1995, Weigle et al., 1997) Treating with leptin increases LH secretion, restores female cyclicity and improves fertility (Ahima et al., 1996, Nagatani et al., 1998, Gonzalez et al., 1999, Watanobe et al., 1999b, Donato et al., 2009). In humans with low energy stores, leptin increases LH, estradiol, and ovarian volume and the number of dominant follicles (Licinio et al., 1998, Miller et al., 1998, Warren et al., 1999, Welt et al., 2004, Chan and Mantzoros, 2005).

Leptin-deficient (*ob/ob*) mice are infertile, although some degree of reproductive success has been reported in young *ob/ob* males (Lane and Dickie, 1954). Leptin replacement in *ob/ob* mice induces sexual development and permits normal fertility (Barash et al., 1996, Chehab et al., 1996, Mounzih et al., 1997). It is important to note that the infertile phenotype of leptin-deficient mice is dependent on genetic background since *ob/ob* mice crossed onto a BALB/cJ strain have improved fertility and are leaner, suggesting the action of unknown modifier genes regulating leptin's effect in metabolism and reproduction (Qiu et al., 2001). In humans, leptin signaling deficiency caused from genetic mutations is rare. Nonetheless, affected individuals are hyperphagic, morbidly obese, do not undergo a pubertal growth spurt and do not reach sexual maturation (Clement et al., 1998, Farooqi et al., 2007, Licinio et al., 2007, Mazen et al., 2009, Fischer-Posovszky et al., 2010, Galgani et al., 2010, Paz-Filho et al., 2010, Fatima et al., 2011, Mazen et al., 2011). Leptin administration to leptin-deficient subjects restores fertility (Farooqi et al., 2002, Farooqi and O'Rahilly, 2006). Therefore, it is accepted leptin acts as a permissive signal for the onset of puberty and maintenance of reproductive function. However, the mechanisms and brain circuitry engaged by leptin regulating reproductive function are not entirely known. This review will focus on recent progress made implicating potential neuronal populations mediating leptin's regulation of reproductive function.

2. Search for Leptin's Target Site(s) for Reproductive Control

The leptin receptor is a member of the class I cytokine receptor family and six isoforms have been identified. Of these six isoforms, the long-form (LepRb) contains JAK-STAT signaling capability and shows a high level of expression in the hypothalamus (Tartaglia et al., 1995,

Chua et al., 1996, Lee et al., 1996, Ahima and Flier, 2000). LepRb expression is also seen in peripheral targets required for reproductive function. In granulosa cells, LepRa and LepRb mRNA levels increase after human chorionic gonadotropin (hCG) treatment and antagonizing leptin receptors during hCG treatment leads to a reduction in oocytes collected from oviducts (Dupuis et al., 2014). Studies using genetically modified mice however have revealed that leptin's effects on metabolism and reproduction are relayed primarily through the brain (Cohen et al., 2001, de Luca et al., 2005, Quennell et al., 2009). Thus, multiple routes do exist for leptin signaling to regulate fertility. However, LepRb signaling via neural targets alone is sufficient for reproductive function. Dense LepRb expression in the hypothalamus along with leptin's role in increasing frequency of LH pulses initially suggested that leptin acted directly on gonadotropin-releasing hormone (GnRH) neurons (Yu et al., 1997, Lebrethon et al., 2000, Parent et al., 2000, Wojcik-Gladysz et al., 2009). However, virtually no LepRb has been detected in GnRH neurons and the deletion of the *Lepr* gene from GnRH cells produces no reproductive deficit (Quennell et al., 2009, Donato et al., 2011a, Louis et al., 2011). Together, these findings suggest that leptin acts on interneurons to stimulate GnRH secretion (Quennell et al., 2009). Proteins downstream of LepRb signaling involved in regulating fertility have also been investigated. Apart from the STAT3 and STAT5 genes, whose respective phosphorylated proteins act as markers for LepRb activation and mediate gene transcription, alternative downstream signaling proteins are now believed to mediate leptin's effects in reproductive function. Studies have revealed that deletion of STAT3 and STAT5 from LepRb expressing cells in mice did not produce any reproductive abnormalities despite the severely deregulated metabolic phenotype (Singireddy et al., 2013).

3. Glutamate and Nitric Oxide from the Ventral Premammillary Nucleus

A concentrated expression of LepRb exists in the ventral premammillary nucleus (PMV). This nucleus responds directly to leptin seen by the induction of Fos immunoreactivity and phosphorylation of STAT3 after leptin treatment. A high percentage of PMV neurons are also depolarized after leptin treatment (Elmquist et al., 1998, Elias et al., 2000, Leshan et al., 2009, Louis et al., 2011, Williams et al., 2011b). Studies in our laboratory have shown that endogenous re-expression of LepRb only in the PMV is sufficient to induce puberty and improve fertility in LepRb-null female mice (Donato et al., 2011b). In addition, bilateral lesions of the PMV impair female reproductive function and prevent the leptin-mediated increase in LH during fasting (Donato et al., 2010, Donato et al., 2011b). These studies reveal an important role the PMV may have in relaying leptin signaling to the HPG axis. However, how this nucleus integrates leptin signaling to stimulate LH secretion is not entirely known. Using standard neuroanatomical techniques and molecular mapping, several laboratories have shown that neurons within the PMV (including those expressing LepRb) project directly to GnRH cells (Rondini et al., 2004, Boehm et al., 2005, Leshan et al., 2009, Donato et al., 2011b, Louis et al., 2011). These projecting neurons express glutamate and therefore may directly activate their terminal targets including GnRH or, alternatively, Kisspeptin-expressing cells (Brann and Mahesh, 1994, Mahesh and Brann, 2005, Donato et al., 2011b).

LepRb neurons within the PMV also co-express neuronal nitric oxide synthase (nNOS) and inhibiting NOS in hypothalamic explants attenuates leptin-induced LH secretion (Yu et al., 1997, Leshan et al., 2009, Donato et al., 2010, Leshan et al., 2012). Whether this leptin mediated NO signaling influencing LH secretion originates from the PMV is unknown. LepRb and nNOS co-localization however is highest in the PMV and in a recent study, LepRb deletion from nNOS expressing neurons delayed pubertal maturation in female mice (Leshan et al., 2012). It is important to point out though that removal of LepRb from other hypothalamic nuclei co-localizating LepRb and nNOS (i.e. the dorsomedial, the ventromedial, the arcuate and the posterior nuclei) may also have a role in the observed delay in pubertal maturation.

4. Kisspeptin Neurons in the Arcuate Nucleus

Kisspeptins (products of the *KISS1/Kiss1* gene) are key regulators of reproductive function (Popa et al., 2008, Colledge, 2009, Oakley et al., 2009, Tena-Sempere, 2010, De Bond and Smith, 2014). Loss-of-function mutations in *KISS1/Kiss1* or Kisspeptin receptor (*GPR54/Gpr54* also known as *KISS1R/Kiss1r*) genes cause infertility, prevent sexual maturation and lead to hypogonadotropic hypogonadism in mice and humans (de Roux et al., 2003, Seminara et al., 2003, d'Anglemont de Tassigny et al., 2007, Lapatto et al., 2007, Topaloglu et al., 2012). Kiss1 mRNA expression and kisspeptin production decreases in conditions of low leptin levels as observed in *ob/ob* mice or wild types in fasting conditions (Castellano et al., 2005, Smith et al., 2006, Luque et al., 2007, Kalamatianos et al., 2008, Quennell et al., 2011). Furthermore, it has been shown in rodents that a subpopulation of Kiss1 neurons in the arcuate nucleus co-express LepRb (Smith et al., 2006, Cravo et al., 2011, Louis et al., 2011, Qiu et al., 2011, True et al., 2011). Male streptozotocin (STZ) rats, which have undergone pancreatic β cells destruction, develop diabetes and show decreased circulating levels of leptin, sex steroids and LH as well as a reduction in Kiss1 mRNA (Castellano et al., 2006). Treating with leptin reverses these effects, identifying a possible role for leptin in restoring Kiss1 mRNA expression during states of negative energy balance and a possible pathway for activating the HPG axis. Our lab generated two genetically modified mouse models to test this idea. In one model, LepRb signaling was deleted from kisspeptin expressing cells, which lead to no reproductive deficits in male and female mice (Donato et al., 2011b). In the second model, functional LepRb was re-activated in kisspeptin cells and from this model it became clear that co-localization of LepRb and kisspeptin occurred only after pubertal maturation. This observation revealed leptin action directly on kisspeptin neurons is not required for pubertal development (Donato et al., 2011b, Cravo et al., 2013). These findings indicate leptin's permissive effect on reproduction does not require direct signaling onto kisspetin neurons, but whether kisspeptin neurons are downstream of leptin's effect still needs to be determined.

5. Melanocortin System and GABAergic Neurotransmission

POMC and AgRP/NPY neurons express LepRb and are important targets mediating leptin's effect on metabolism and food intake (Elmquist et al., 1999, Mizuno and Mobbs, 1999, Cone et al., 2001, Morrison et al., 2005, Woods and D'Alessio, 2008, Williams et al., 2011a). Several laboratories have indicated that this neuronal network plays a role in

reproductive function. However, inconsistencies exist among species on whether leptin targets within the melanocortin system regulate reproductive function. For example, loss-of-function mutations of melanocortin signaling in humans does not lead to reproductive dysfunction (Krude et al., 1998, Yeo et al., 1998, Farooqi and O'Rahilly, 2006). However, studies in seasonal breeders (e.g. ewes) suggest that melanocortins mediate leptin's regulatory effect on fertility (Backholer et al., 2009, Backholer et al., 2010).

Melanocortin fibers (originating from POMC or AgRP neurons) densely innervate the preoptic area and make synaptic contact with GnRH and kisspeptin neurons (Leranth et al., 1988, Broberger et al., 1998, Cravo et al., 2011). In rats, α-melanocyte stimulating hormone (αMSH) may stimulate or inhibit LH secretion depending on sex steroids levels (Celis, 1985, Scimonelli and Celis, 1990). Loss-of-function mutations in *Pomc* or melanocortin receptor (*Mc3r* or *Mc4r*) genes lead to obesity and subfertility (Huszar et al., 1997, Butler and Cone, 2002, Cone, 2005). Moreover, mice with ubiquitous expression of the agouti protein (Ay) – an antagonist of melanocortin receptors – are obese and show disrupted cyclicity (Granholm et al., 1986). AgRP exerts a similar antagonistic effect on melanocortin receptors (Ollmann et al., 1997, Hahn et al., 1998). AgRP treatment or blockade of MC4R decreases the LH surge in ovariectomized steroid-primed female rats (Watanobe et al., 1999a, Schioth et al., 2001) and suppresses LH levels in ovariectomized rhesus monkeys (Vulliemoz et al., 2005). However, in male rats AgRP stimulates GnRH secretion from hypothalamic explants and increases circulating gonadotropins in vivo (Stanley et al., 1999). In fasted female rats, MC4R antagonists decrease the ability of leptin to stimulate LH secretion (Watanobe et al., 1999b). However, pharmacological blockade of MC4R does not prevent leptin from restoring reproductive capacity in *ob/ob* male mice (Hohmann et al., 2000). Deletion of LepRb from either POMC neurons or AgRP neurons, or a simultaneous POMC and AgRP deletion of LepRb, does not cause reported reproductive deficits (Balthasar et al., 2004, van de Wall et al., 2008). Studies from independent laboratories however have shown that ablation of AgRP neurons or deletion of one allele of *Mc4r* gene improved the infertility phenotype of leptin-signaling deficient mice (Israel et al., 2012, Wu et al., 2012, Sheffer-Babila et al., 2013). Together, these findings indicate that leptin action in melanocortin neurons is not required for the development and maturation of the reproductive system in mice but blockade of AgRP or melanocortin signaling is sufficient to improve fertility in leptin-signaling deficient mouse models.

As mentioned, AgRP neurons coexpress NPY, a neuropeptide elevated in *ob/ob* mice as well as in conditions of negative energy balance including fasting, excessive exercise and lactation (Smith, 1993, Qu et al., 1996, Ahima et al., 2000, Schwartz and Porte, 2005, Woods and D'Alessio, 2008). High NPY expression in the arcuate nucleus may contribute to the reproductive deficits observed in these conditions (Aubert et al., 1998). It was shown that deletion of the *Npy* gene improves the metabolic and infertility phenotype of *ob/ob* mice (Erickson et al., 1996). However, interestingly, NPY knockout mice and mice with LepRb deletion from NPY/AgRP neurons display normal reproductive function (Erickson et al., 1996, van de Wall et al., 2008). It will be important to assess if improvement of fertility of the $NPY^{-/-}$ *ob/ob* mice is secondary to the decreased hyperglycemia and reduced adiposity.

AgRP neurons co-express the neurotransmitter GABA (Tong et al., 2008, Wu and Palmiter, 2011, Krashes et al., 2013). Recent studies have demonstrated that deletion of LepRb from GABAergic neurons cause severe obesity and metabolic dysfunction (Vong et al., 2011). These mice show impaired reproductive function as well, indicating that leptin signaling in GABAergic neurons is required for normal fertility in mice. It was also shown that removing leptin signaling from glutamatergic neurons did not produce any reproductive deficits regardless of the slightly abnormal metabolic phenotype (Zuure et al., 2013, Martin et al., 2014). These observations may seem unexpected, due to the data collected from reactivating LepRb in glutamatergic PMV neurons discussed in previous sections; however a critical look may reconcile the findings. Leptin signaling in glutamatergic PMV neurons is sufficient but may not be required for reproduction. Following the same idea, it still needs to be assessed whether leptin action in GABAergic neurons is sufficient to induce puberty and improve fertility in LepR-null mice. Also, the population of GABAergic neurons mediating the positive effects on fertility needs to be defined. The co-localization of GABA and AgRP in arcuate nucleus neurons and the improvement of fertility in *ob/ob* mice following their ablation, indicate that AgRP/GABA neurons are prime candidates for relaying leptin signaling to the HPG axis.

6. Conclusion

The role of leptin, the product of the *ob* gene as defined in the *ob/ob* mouse, as a metabolic signal of energy sufficiency has been known for decades. However, the brain circuitry and signaling pathways involved in this specific action of leptin have been difficult to determine due to the lack of scientific tools. The development of new mouse models and genetic strategies to conditionally manipulate genes of interest has produced an abundance of relevant new findings in the field. The roles of glutamatergic neurons in the PMV, of the AgRP neurons in the arcuate nucleus and the requirement of leptin signaling via GABAergic neurons have been revealed (fig.1). However, the complete pathway is far from being defined. For instance, whether GABA neurotransmission or glutamate and NO from PMV neurons are necessary for leptin's effects on fertility is yet to be demonstrated. It is also not known if these neurons converge directly onto GnRH cells or use an alternative pathway via actions in upstream neuronal populations (e.g. kisspeptin neurons). Pursuing these questions will lead to new opportunities for addressing decreased fertility caused by metabolic imbalances and will generate a greater understanding of the central control of reproductive function.

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Highlights

- Leptin's effects in reproduction are mediated by hypothalamic neurons.
- Leptin's action in glutamatergic ventral premammilary (PMV) neurons is sufficient for female fertility.
- Leptin's action in Kiss1 neurons is neither required nor sufficient for fertility.
- Ablation of AgRP neurons improves fertility of *ob/ob* mice.
- GABAergic first order neurons play a key role in leptin's action on reproduction.

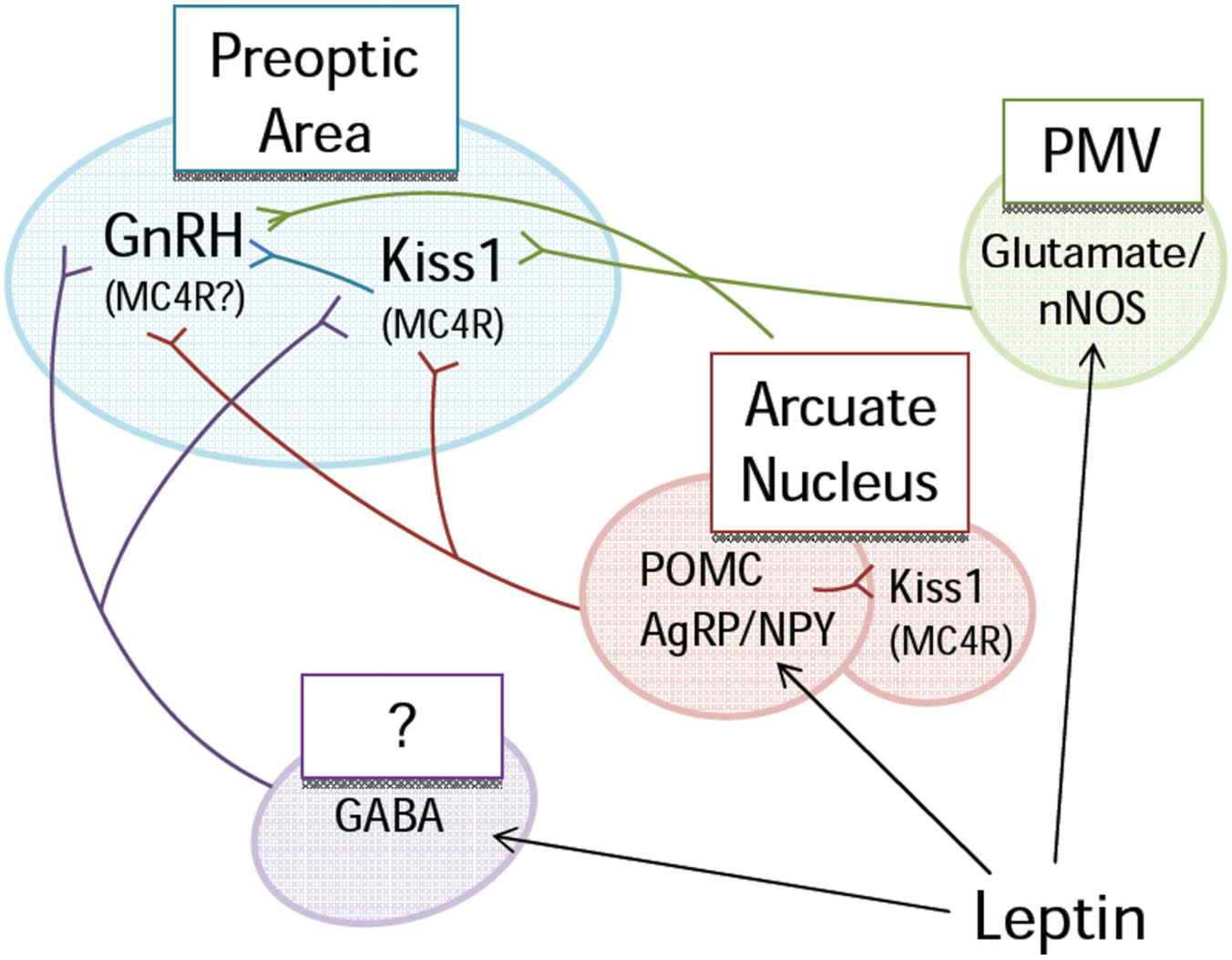

Fig. 1.

Illustration of chemically identified hypothalamic routes engaged by leptin in reproductive control. POMC and AgRP/NPY neurons in the arcuate nucleus express LepRb and project to the preoptic area where MC4Rs are expressed on Kisspeptin neurons and possibly GnRH neurons. Leptin responsive Glutamatergic PMV neurons co-expressing nNOS project to GnRH neurons and to the preoptic area in the vicinity of AVPV Kiss1 neurons. In the preoptic area Kiss1 neurons act directly on GnRH neurons.Leptin acts on unidentified GABAergic neurons which may project directly to GnRH, Kiss1 or unidentified interneurons.