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REVIEW ARTICLE

Regulation of gonadotropin secretion by monitoring energy availability

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Abstract Nutrition is a principal environmental factor influencing fertility in animals. Energy deficit causes amenorrhea, delayed puberty, and suppression of copulatory behaviors by inhibiting gonadal activity. When gonadal activity is impaired by malnutrition, the signals originating from an undernourished state are ultimately conveyed to the gonadotropin-releasing hormone (GnRH) pulse generator, leading to suppressed secretion of GnRH and luteinizing hormone (LH). The mechanism responsible for energetic control of gonadotropin release is believed to involve metabolic signals, sensing mechanisms, and neuroendocrine pathways. The availabilities of blood-borne energy substrates such as glucose, fatty acids, and ketone bodies, which fluctuate in parallel with changes in nutritional status, act as metabolic signals that regulate the GnRH pulse generator activity and GnRH/LH release. As components of the specific sensing system, the ependymocytes lining the cerebroventricular wall in the lower brainstem integrate the information derived from metabolic signals to control gonadotropin release. One of the pathways responsible for the energetic control of gonadal activity consists of noradrenergic neurons from the solitary tract nucleus in the lower brainstem, projecting to the paraventricular nucleus of the hypothalamus. Further studies are needed to elucidate the mechanisms underlying energetic control of reproductive function.

Keywords Energy sensor · Gonadotropin · Metabolic signal · Neuroendocrine pathway · Nutrition

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Introduction

In mammals, the reproductive system is essential for preservation of the species, but not for organismal survival. Consequently, in order to maximize the chances that offspring will survive, reproductive function in mammals is influenced by a wide variety of environmental factors. For instance, when animals find themselves in life-threatening situations, reproductive function is suppressed because preservation of the individual organism's life has the highest priority. Improvement of such situations restores reproductive function to ensure the next generation. Changes in nutritional status have a profound impact on fertility in animals, because energy deficiency is one of the critical situations for their lives [1]. Indeed, energy deficit due to weight loss, excessive exercise, eating disorders, or dietary restriction causes functional hypothalamic amenorrhea through the disruption of neuroendocrine axes in both women [2–5] and rhesus monkeys [6]. During the prepubertal period, puberty is delayed in nutritionally growth-restricted female rats [7, 8] and sheep [9, 10], and the onset of puberty begins when food intake is increased. In dairy cows, under-nutrition with high milk yields is associated with delayed resumption of ovarian activity after parturition and lower conception rates [11]. Furthermore, women with insulin-dependent diabetes mellitus, a condition in which cells are starved for energy even if blood glucose level is high [12], often exhibit menstrual dysfunction [13]. As illustrated by these examples, the correlation between fertility and nutrition has been extensively studied for a long time. However, the mechanisms underlying nutritional control of reproductive function are not yet fully understood. Here, we describe the mechanisms responsible for energetic control of reproductive function, which involve a number of components,

including metabolic signals, sensing mechanisms, and neuroendocrine pathways.

Neuroendocrine mechanism regulating reproductive function

Animal reproduction is regulated by the hypothalamic–pituitary–gonadal (H–P–G) axis, and gonadotropin-releasing hormone (GnRH) is a key determinant of gonadal activity [14] (Fig. 1). GnRH is a decapeptide synthesized by the GnRH neurons in the hypothalamus, whose fibers converge in the median eminence (ME). GnRH is released into the hypophyseal portal vessels from the nerve terminals in the ME, and it regulates the synthesis and release of two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the anterior pituitary. These gonadotropins control gonadal activity such as spermatogenesis, follicular development, ovulation, and sex steroid hormone synthesis. The sex steroid hormones, in turn, act on the hypothalamus and pituitary to regulate GnRH and gonadotropin secretion by positive or negative feedback.

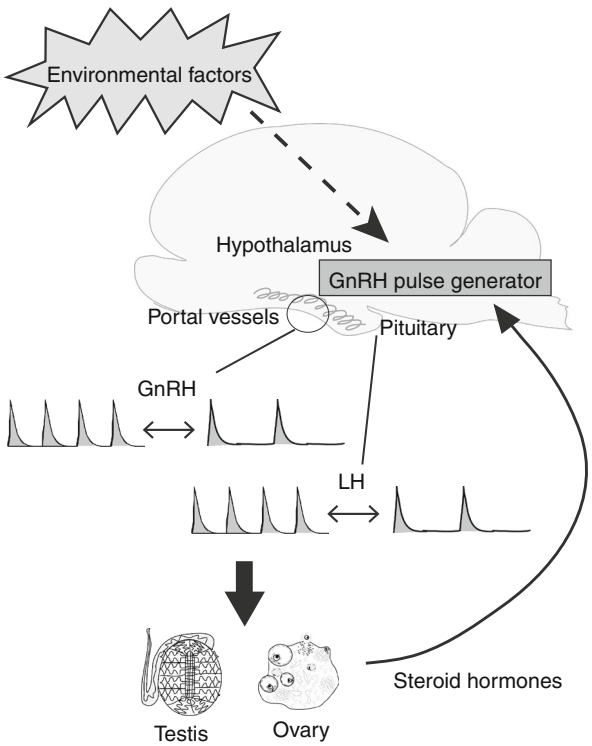

Fig. 1 Schematic illustration of the hypothalamic–pituitary–gonadal axis in mammals. Signals originating from various environmental factors are finally conveyed to the gonadotropin-releasing hormone (GnRH) pulse generator. These signals affect the GnRH pulse generator's activity, thereby regulating pulsatile GnRH and luteinizing hormone (LH) secretion, which in turn control gonadal activities

GnRH is released in a pulsatile pattern at regular intervals in rhesus monkeys [15]. In rhesus monkeys with electrolytic lesions of the hypothalamus that abolish endogenous gonadotropin release from the pituitary gland, an intermittent administration of exogenous GnRH at a physiological frequency reestablishes normal pituitary gonadotropin secretion, whereas continuous infusion of GnRH fails to restore gonadotropin secretion [16]. Thus, the pulsatile pattern of GnRH release from the hypothalamus is indispensable for the function of the H–P–G axis, and it is therefore likely that gonadal activity is regulated by the frequency of GnRH pulses rather than the quantity of GnRH released. LH is also secreted in a pulsatile pattern at regular intervals [17–20], and the temporal relationships between GnRH and LH pulses have been well documented in monkeys [21–23], ewes [24–26], and rats [27, 28]. Accordingly, pulsatile LH secretion has been used as a parameter of fertility.

Pulsatile GnRH secretion is required to synchronize release of GnRH from individual nerve terminals and coordinate activation of GnRH neurons by neuronal afferents. The distinct neural circuitry in the hypothalamus, termed the "GnRH pulse generator", is generally believed to possess several characteristics: generation of rhythmic oscillations, electrophysiological synchronization, transmission of the signal of rhythmic oscillation to GnRH neurons, and elicitation of a pulsatile GnRH discharge [29]. Therefore, the GnRH pulse generator is accepted to be the most significant center involved in regulation of reproductive function. Based on the discoveries of kisspeptin and subsequently of KNDy (kisspeptin/neurokinin B/dynorphin) neurons in the hypothalamus, it has been proposed that KNDy neurons in the hypothalamic arcuate nucleus play a pivotal role in the generation of GnRH pulses [30, 31]. In other words, it is possible that the KNDy neurons constitute the GnRH pulse generator.

The GnRH pulse generator plays the most pivotal role in regulating fertility in proportion to changes in environmental factors such as photoperiod, temperature, nutrition, stressors, and pheromones (Fig. 1). For instance, in the energetic control of reproductive function, nutritional status is transmitted to the GnRH pulse generator and affects its activity through various signals. The activity of the putative GnRH pulse generator can be monitored as the multiple unit activity (MUA) by recording the electrical activity of several neurons around an electrode implanted in the mediobasal hypothalamus. Because periodic bursts of MUA (termed "MUA volleys") are temporally correlated with LH pulses in peripheral circulation, the interval of MUA volleys is reflected in the GnRH pulse generator activity. The MUA recording technique can directly assess the effects of various environmental factors on the GnRH pulse generator in conscious animals, in real time, and over long periods.

Energetic influence on reproductive functions

Nutrition is a principal factor influencing fertility in mammals. Inadequate nutritional status impairs gonadal activity, which in turn induces reproductive difficulties in many animals, and nutritional infertility manifests itself in a variety of ways. Most typically, nutritional infertility is expressed as delayed puberty in juveniles [10, 32], prolonging postpartum anestrus [33] and suppressing ovulatory cycles and copulatory behaviors in adults [34]. Short-term food deprivation suppressed the activity of the GnRH pulse generator by prolonging the intervals of MUA volleys in goats [35, 36] and pulsatile LH secretion in sheep [37], rats [38], and monkeys [39]. Chronic food restriction also prevents the pulsatile LH secretion in sheep [10, 39, 40]. Growth-retarded hypogonadotropic lambs, induced by dietary restriction, also exhibited reduced pulsatile GnRH release [41]. These facts indicate that the signal originating from the undernourished state is ultimately conveyed to the GnRH pulse generator and induces the suppression of pulsatile GnRH and LH secretion, which in turn impairs gonadal activity.

Metabolic substrates as energetic regulators of reproductive function

Several lines of evidence have revealed that changes in the availability of blood-borne energy substrates such as glucose and fatty acids are related to changes in pulsatile GnRH and LH release and gonadal activity [42–47] (Fig. 2).

Pharmacological glucoprivation induced by administration of 2-deoxy-D-glucose (2DG) suppresses pulsatile LH secretion in rats [48, 49]. Similarly, insulin-induced hypoglycemia inhibits pulsatile LH secretion in rats [50, 51] and monkeys [52, 53]. In ruminants, pulsatile LH secretion is also suppressed by insulin-induced hypoglycemia [54, 55] and 2DG-induced glucoprivation [56]. Studies using the MUA recording method have revealed that the activity of the GnRH pulse generator in goats is suppressed by 2DG-induced glucoprivation or insulin-induced hypoglycemia [57]. Based on these results, alternation of glucose availability is considered to be an important energetic regulator of GnRH pulse generator activity. Moreover, Ohkura et al. [57] demonstrated that GnRH pulse generator activity responds sharply to changes in glucose availability, suggesting that the activity of the GnRH pulse generator is fine-tuned and sensitive to slight fluctuations in glucose availability.

Pharmacological blockade of the oxidation of fatty acids, another blood-borne energy substrate, eliminates estrous cyclicity and sexual behavior in rats and hamsters [43, 45]. Acute lipoprivation induced by peripheral administration of mercaptoacetate (MA), an inhibitor of fatty acid oxidation, suppresses pulsatile LH secretion in female rats [58]. According to these observations, the availability of fatty acids could be an additional energetic signal that regulates reproductive function. In addition, the inhibition of pulsatile LH release by lipoprivation with MA is more severe in fasted animals than ad libitum-fed animals [58], suggesting that availability of fatty acids may be more indispensable for maintenance of reproductive function, especially when fatty acids are a major fuel source under energy-deficient conditions. On the other hand, peripheral administration of MA does not affect GnRH pulse generator activity in goats [57], suggesting that fatty acid oxidation may not be a regulator of GnRH pulse generator activity in this species. The inconsistency in the effects of lipoprivation between rats and goats may be due to differences in these animal models: rats are monogastrics, whereas goats are ruminants, and the two species consequently have different pathways for energy metabolism.

In ruminants, other metabolites such as volatile fatty acids (VFAs) are the major energy substrates. VFAs such as butyric acid, propionic acid, and acetic acid are derived

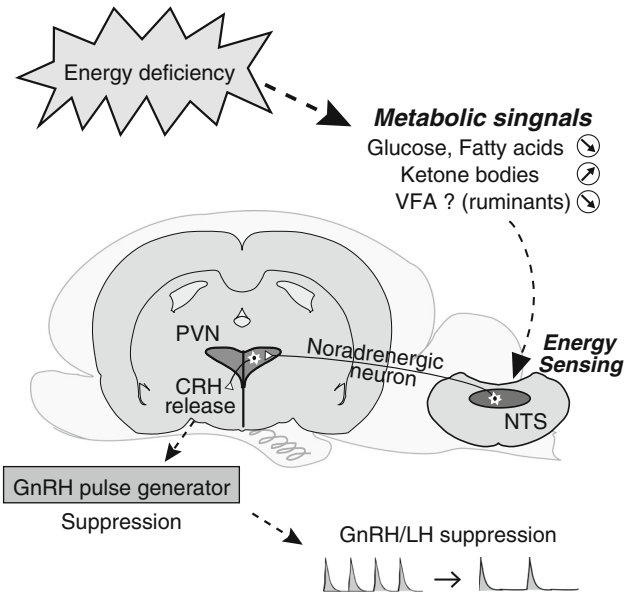

Fig. 2 Possible neuroendocrine mechanism for the energetic control of reproductive function. During energy deficiency, low glucose and fatty-acid availabilities and high ketone-body availability are sensed by the ependymocytes in the solitary tract nucleus (NTS). Information about energy status activates noradrenergic neurons in the paraventricular nucleus (PVN), projected from the NTS. The resultant neural activity inhibits gonadotropin-releasing hormone (GnRH) pulse generator activity, and thereby suppresses GnRH/luteinizing hormone (LH) secretion, via elevated release of corticotropin releasing hormone (CRH)

from microbial fermentation in the rumen. Supplementation of a maintenance diet with VFAs stimulates pulsatile LH secretion in sheep [59], suggesting that VFAs play some role in the regulation of reproductive function. Although utilization of VFAs as metabolic fuels is a distinctive feature of ruminants, butyric acid and propionic acid are converted to ketone bodies [60] and glucose [61], respectively. By contrast, acetic acid is not converted to another substrate but is itself used as a metabolic fuel in ruminants. During 4-day fasting in goats, the plasma acetic acid concentration decreases, and this change accompanies the suppression of GnRH pulse generator activity [36]; the restoration of the GnRH pulse generator activity during the subsequent re-feeding period is coincident with the recovery of plasma acetic acid concentrations to the pre-fasting levels. Therefore, it is possible that the availability of acetic acid is a ruminant-specific signal that controls the GnRH pulse generator activity.

Ketone bodies, a general term for acetone, acetoacetate, and 3-hydroxybutyrate (3HB), are present at higher levels in circulating blood of undernourished animals, due to acceleration of fatty acid oxidation in the liver. During energy deficiency, uptake of ketone bodies into the brain is increased [62–64], where ketone bodies are primarily utilized as an alternative to glucose [64–66]. Diabetes mellitus causes enhanced fatty acid oxidation and ketosis, and reproductive dysfunction often occurs in women with type 1 diabetes [13, 67]. Both the suppression of GnRH pulse generator activity during fasting in goats [36] and the low-LH pulse frequency during early postpartum periods in dairy cows [68] are concomitant with increases in plasma 3HB concentrations. In addition, central injection of 3-HB suppresses pulsatile LH secretion in rats [69] and GnRH pulse generator activity in goats (unpublished data). Accordingly, it has been proposed that ketone bodies, which are overproduced during energy deficiency, may function as a negative energy signal on the regulation of reproductive function.

Energy availability sensing in the brain

In order to control feeding, reproduction, and energy homeostasis, the brain integrates information derived from changes in blood levels of energy substrates through specific sensing systems. Electrolytic lesions of the lateral hypothalamic nucleus (LHA) and ventromedial hypothalamic nucleus (VMH) in the hypothalamus cause anorexia and hyperphagia, respectively, in rats and cats [70]. Based on this result, the LHA and VMH in the hypothalamus have been classically considered to be the feeding and satiety centers, respectively. Moreover, neurons in the LHA and VMH respond to hyper- or hypoglycemic stimulation in rats [71, 72] and cats [73]. On the other hand, several lines of evidence suggest that glucose sensors involved in feeding and the gonadal axis are located outside of the hypothalamus, in particular in the hindbrain [46]. The injection of 5-thioglucose (5TG), a potent antimetabolic glucose analogue, into the fourth ventricle but not the lateral ventricle causes increased food intake and hyperglycemia in rats in which cerebrospinal fluid flow has been blocked by silicon glue in the aqueduct [74]. Local implantation of 5TG in the ventrolateral and dorsomedial medulla, but not in the hypothalamus, induces food intake and hyperglycemic response [75]. Administration of 2DG into the fourth ventricle suppresses pulsatile LH secretion in rats [48] and sheep [56]. All of these studies strongly suggest that a glucose sensor involved in control of feeding and reproductive function is located in the lower brainstem (Fig. 2).

What kinds of cells in the lower brainstem monitor the changes in glucose availability? Because pancreatic β-cells control insulin secretion in response to changes in plasma glucose concentrations, they are accepted to be equipped with a glucose-sensing system. In particular, glucose transporter 2 (GLUT2) and glucokinase (GK) in pancreatic β-cells have been proposed to play a critical role in sensing blood glucose levels. GLUT2 is one of several isoforms of GLUTs, which are embedded in the plasma membrane; these transporters uptake glucose molecules into the cytoplasm in order to initiate glucose oxidation inside the cell. GK, also called hexokinase IV, converts glucose to glucose-6-phosphate after cellular glucose uptake. GLUT2 and GK are distinguished from other GLUTs and hexokinases, respectively, by their low affinities for glucose and high Km values, which are relatively close to the physiological range of blood glucose levels [76, 77]. Furthermore, because pancreatic GK activity is not inhibited by glucose-6 phosphate, changes in GK-mediated glucose phosphorylation always parallel extracellular glucose levels [78]. Thus, GK activity is proportional to the blood glucose level, and it could therefore contribute to sensing of glucose levels.

Several studies have revealed that pancreatic GK protein and mRNA are expressed in the brain [79–85]. In particular, immunoreactivity to pancreatic GK can be detected in the wall of third ventricle [79], and GK mRNA is expressed in hypothalamic nuclei, include in the VMH, in rats [81, 82]. These observations support the classical idea that neurons in the satiety and feeding centers of the hypothalamus play pivotal roles in the glucose-sensing mechanism. On the other hand, in the hindbrain of rats, particularly in the lower brainstem, immunoreactivities to pancreatic GK and GLUT2 [83] and the expression of pancreatic GK mRNA [86] can be detected in the ependymocytes lining the wall of the fourth ventricle. Thus, the

ependymocytes in the lower brainstem could monitor glucose levels in the cerebrospinal fluid in order to control physiological functions. Administration of alloxan, a specific GK inhibitor, into the fourth ventricle suppresses pulsatile LH secretion in rats [87]. In addition, GK-containing ependymocytes of the cerebroventricular wall in the lower brainstem increase intracellular calcium concentrations in response to changes in extracellular glucose concentrations in vitro [86]. These results lead us to the idea that GK-containing ependymocytes in the lower brainstem are involved in the glucose-sensing mechanism that controls gonadal activity.

The localizations of the sensors of fatty acid and ketone bodies have also been investigated in the context of regulation of reproductive functions. Fourth-ventricular injection of MA or trimetazidine, inhibitors of fatty acid oxidation, inhibits pulsatile LH release, suggesting that fatty-acid availability is sensed in the lower brainstem to control gonadotropin secretion in rats [88]. In the regulation of feeding, it is possible that fatty-acid availability is detected by peripheral sensors. The increase in food intake induced by intraperitoneal injection of MA is abolished by subdiaphragmatic vagotomy [89]. In addition, induction of Fos-like immunoreactivity in the rat brain by MA is blocked by vagotomy [90]. On the other hand, vagotomy does not eliminate the lipoprivation-induced anestrus in fat fasted hamsters [91], and lipoprivic LH inhibition is not blocked by the vagotomy [58]. These studies raise the possibility that lipoprivation induces feeding through a peripheral sensor, but suppresses reproductive functions through a central sensor in the lower brainstem (Fig. 2).

Proton-coupled monocarboxylate transporters (MCTs) are indispensable for transport of ketone bodies into the cell [92, 93]. Immunoreactivity to MCT1, which is the major isoform of MCTs, can be detected in the ependymocytes around the fourth ventricle in rats [94]. Moreover, injections of pCMBS, an MCT1 inhibitor, into the fourth ventricle normalizes hyperphagia in diabetic rats. CSF 3HB levels are elevated in diabetic rats, and positively correlated with plasma 3HB levels. Administration of 3HB into the fourth ventricle suppresses pulsatile LH secretion [69] and increases food intake [94] in rats. Based on these facts, ketone bodies in the CSF are likely to be sensed in the ependymocytes of the lower brainstem, through MCT1, in order to control feeding and reproductive functions.

Neuroendocrine pathway mediating energetic regulation of gonadotropin release

The dominant noradrenergic neurons from the lower brainstem, including the solitary tract nucleus (NTS), project to the paraventricular nucleus (PVN) of the hypothalamus [95]. Moreover, noradrenaline released in the PVN activates corticotropin-releasing hormone (CRH) neurons, and then increases their release into the portal circulation [96]. Based on these lines of evidence, it has been studied the neural pathway in the brain that mediates suppression of GnRH/LH pulses in response to decreased availability of several energetic substrates. Peripheral administration of 2DG induces Fos-like immunoreactivity in the NTS and PVN of rats [90]. The suppression of pulsatile LH secretion induced by administration of 2DG is associated with an increase in noradrenaline in the PVN of rats [97]. In addition, administration of noradrenaline into the PVN suppresses the pulsatile LH secretion in rats, whereas pretreatment with α-helical CRF, an antagonist of CRH, in the third ventricle blocks this inhibition [98]. The inhibitory effect of 2DG administration on LH pulses can also be prevented by the intracerebroventricular injection of α-helical CRF in rats [99]. The administration of MA [88] and 3HB [69] into the fourth ventricle also suppresses LH pulses and increases noradrenaline release in the PVN. Moreover, injection of a catecholamine synthesis inhibitor or α1-, α2-adrenergic receptor antagonist into the PVN blocks the suppressive effect of MA and 3HB injections on LH pulses [69, 88, 100]. Taken together, these data suggest that the noradrenergic pathway from the NTS to the PVN is involved in the glucoprivic suppression of pulsatile LH secretion. It is possible that low glucose and fatty-acid availabilities in conjunction with high ketone-body availability, all of which are sensed by the ependymocytes in the lower brainstem, activate noradrenergic neurons in the PVN, which receive projections from the NTS, and inhibits LH secretion by increasing CRH release (Fig. 2).

The suppression of pulsatile LH secretion induced by 2DG-induced glucoprivation, MA-induced lipoprivation, or administration of 3HB is enhanced by estrogen. In rats, glucoprivation induces an increase in estrogen receptor α (ERα) expression in the PVN and the brainstem [101], and the induction of ERα expression in the PVN could be mediated by the catecholaminergic inputs to the PVN from the brainstem [102]. Thus, it is possible that the increases in ERα expression in these brain areas enable estrogen to potentiate the neural pathway mediating LH suppression via reductions in the availabilities of several energetic substrates. However, further studies will be required to elucidate the action of estrogen on the energetic control of reproductive function.

Summary

In the energetic control of gonadal activity, the availabilities of blood-borne energy substrates such as glucose, fatty acids, and ketone bodies act as metabolic signals to

regulate the GnRH pulse generator activity and GnRH/LH release. These metabolic signals are sensed by specific sensors in the brain, which constantly monitor variations in nutritional status. One of the candidate energetic sensors is located in the lower brainstem. The ependymocytes in the lower brainstem detect the availabilities of glucose and fatty acids as positive energetic factor, and ketone-body availability as negative energetic factor, for the regulation of gonadal activity. The nutritional information received at the ependymocytes is integrated, and then transmitted to the PVN through the noradrenergic pathway from the NTS to control gonadotropin secretion. Further understanding of the mechanisms underlying energetic control of reproductive function is needed in order to treat reproductive difficulty caused by malnutrition.

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Conflict of interest Shuichi Matsuyama and Koji Kimura declare that they have no conflict of interest.

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