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Neuroendocrine mechanism mediating fasting-induced suppression of luteinizing hormone secretion in female rats

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Abstract. Forty-eight hours fasting profoundly suppresses LH secretion in female rats. The following neural pathway mediating fasting-induced suppression of LH secretion has been suggested by a series of experiment: a signal associated with fasting emanating from the upper digestive tract reaches the A2 region in the medulla oblongata *via* afferent vagal nerve so as to activate the noradrenergic pathway projecting to the hypothalamic paraventricular nucleus (PVN); this results in an increased corticotropin-releasing hormone release to suppress LHRH release and then LH release. The PVN and A2 region of the medulla oblongata are the estrogen feedback sites to activate the above-mentioned neural pathway. The estrogen feedback action on the PVN and A2 region is considered to be due to an increased expression of estrogen receptors in these nuclei after 48-h fasting. The response of gonadal axis during fasting could be due to the changes in some nutrients, such as glucose and free-fatty acids. In this context, malnutrition could be a kind of stress accompanied by an increased feeding behavior and decreased gonadal activity.

Mini-review

Key words: fasting, luteinizing hormone, paraventricular nucleus, nucleus of the solitary tract, noradrenaline, estrogen feedback, rat

INTRODUCTION

Stress is known to be an environmental factor affecting the activity of the gonadal axis predominantly by inhibiting LHRH/LH release in various mammalian species (Rivier and Rivest 1991). The neuroendocrine mechanism mediating stress-induced suppression of LHRH/LH has been extensively studied, since Hans Serye (Selye 1952) has first noted that the activity of reproductive system is profoundly suppressed by the stress during his outstanding career of establishing the concept of stress. Corticotropin-releasing hormone (CRH) has been considered to be one of the key molecules for regulating the reproductive activity under a stressful condition (Rivier and Rivest 1991) after its discovery (Vale and Spiess 1981). We have tried to clarify the neuroendocrine mechanism mediating stress-induced suppression of LH secretion using 48-h fasted female rats as a model. Food deprivation has been found to be one of the stressors suppressing LH secretion and then the activity of gonadal axis (Bergendahl et al. 1989, Brady et al. 1990). In our previous studies (Cagampang et al. 1990, 1991), we found that pulsatile LH secretion is profoundly suppressed after 48-h fasting and that the suppression was only observed in intact or ovariectomized estrogen-primed rats but not in ovariectomized animals. The feedback effect of estrogen is dose-dependent and progesterone does not seem to be involved in this feedback action (Cagampang et al. 1991).

In this article, we describe the neural pathway mediating fasting-induced suppression of pulsatile LH secretion and the mechanism by which estrogen feedback activating the neural pathway. We also focus on the nutritional cues, especially glucose availability, as a key factor involved in the fasting--induced suppression of LH secretion.

NEURAL PATHWAY MEDIATING FASTING-INDUCED SUPPRESSION OF LH SECRETION

A series of experiments was conducted to identify the neural pathway mediating fasting-induced suppression of LH secretion in female rats. Wistar--Imamichi rats were ovariectomized and immediately received an estrogen implant to produce basal estrogen level. The animals were then deprived of food for 48 h before blood samplings. Pulsatile LH secretion was used as an indicator for the gonadal axis activity, so that blood samples were collected every 6 min for 3-4 h through an atrial cannula in unanesthesized conscious animals.

An intracerebroventricular injection of CRH receptor antagonist, α-helical CRF (9-41) completely blocked the inhibitory effect of 48-h fasting on pulsatile LH secretion (Maeda et al. 1994), suggesting that the fasting-induced suppression of LH pulses is mediated by CRH release as has been reported in rats bearing other types of stressors (Fig. 1), *such as* foot-shock stress (Rivier et al. 1986). Several lines of evidence have indicated that CRH is a potent inhibitor of LHRH and LH release (Rivier and Vale 1984, Rivest et al. 1993) and the PVN has been

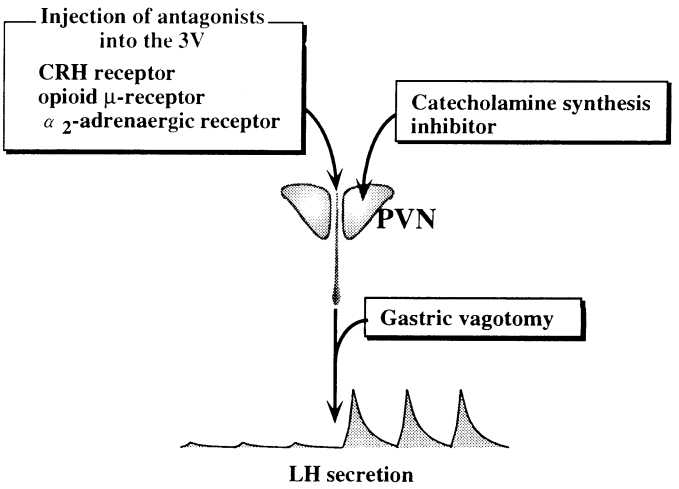

Fig. 1. Summary of the previous results: various treatments on suppressed LH pulses in E2- primed ovariectomized fasted rats. Microinjecton of α-methyl-p-tyrosine (α-MPT) in the paraventricular nucleus (PVN) immediately before the start of samplings blocked the inhibitory effect of fasting on pulsatile LH release. Suppressed pulsatile LH release was immediately restored by intracerebroventricular (icv) injection of naloxone, α-helical CRF or α_2-adrenergic receptor antagonist or by transection of gastric branches of the vagus nerve after the first one hour of the blood sampling. 3V, third ventricle; PVN, paraventricular nucleus; CRH, corticotropin-releasing hormone; LH, luteinizing hormone.

shown to be one of the predominant area where most CRH neuronal cell bodies are located (Mezey and Palkovits 1991). These CRH neurons have been shown to receive noradrenergic inputs from the medulla oblongata (Sawchenko and Swanson 1982), which regulate CRH release (Plotsky 1987). In addition, autoradiographic studies have shown that CRH neurons in the PVN are abundant with $\alpha 1$- and α_2-receptors (Cunningham and Sawchenko 1988). We have actually shown that third ventricle administration of α_2-adrenergic receptor antagonists restored the suppressed LH pulses during fasting (Fig. 1) but α_1- or β-antagonist did not (Cagampang et al. 1992). The result raised a possibility that the noradrenergic input to the PVN induces CRH release through α_2-receptors to suppress LHRH/LH secretion during fasting.

To determine if the noradrenergic pathway projecting to the PVN mediates the effect of fasting on LH secretion, the effect of microinjection of a catecholamine synthesis inhibitor, α-methyl-p-tyrosine (α-MPT), into the PVN on suppressed LH secretion after 48-h fasting was examined in ovariectomized estradiol-primed rats (Maeda et al. 1994). An local injection of α-MPT into the PVN blocked the inhibitory effect of 48-h fasting on LH secretion (Fig. 1), while the same treatment did not affect pulsatile LH secretion in unfasting controls. Taken the result together with previous results, noradrenergic inputs to the PVN mediate the fasting-induced suppression of LH secretion through α_2-receptors. The results also suggest that the PVN α_2 receptors mediating the suppression of LH pulses are postsynaptic, unlike the α_2-receptors in the peripheral nervous system which are known to be presynaptic. Interestingly, postsynaptic α_2-receptors in the PVN has also been found to be involved in the feeding behavior, especially the carbohydrate feeding (Leibowitz 1988). The signals associated with the fasting may be transmitted to the PVN *via* catecholaminergic pathway and integrated in the nucleus to regulate both the feeding behavior and gonadal activity through the α_2 receptors. It reminds us that eating disorders, such as anorexia nervosa, are often accompanied by amenorrhea in women.

The μ-opioidergic receptors could also mediate the effect of fasting on LH pulses, because μ-opioid receptor antagonist, but not κ- or δ-opioid receptor antagonist, restored suppressed LH secretion after 48-h fasting in ovariectomized estradiol-primed rats (Fig. 1) (Cagampang and Maeda 1991). It has been reported that the inhibitory effect of CRH on LH secretion is mediated by endogenous opioids (Gindoff and Ferin 1987, Rivest et al. 1993). Endogenous opioids may be involved in mediating the inhibitory effect of CRH on LH pulses during fasting in female rats.

The vagus nerve has been reported to mediate the satiating effect of CCK-8 and various nutrients such as fatty acids and carbohydrates which are directly applied to the upper digestive tract (Ritter and Taylor 1989). Therefore, the effect of acute transection of various branches of the vagus nerve on suppressed LH release after 48-h fasting was examined in ovariectomized estradiol-primed rats (Cagampang et al. 1991). Total vagotomy by cutting the subdiaphragmatic vagus nerves immediately restored the suppressed LH release during fasting. Vagotomy restricted to gastric branches of the vagus nerve had the similar effect on the LH release to the total vagotomy, but the celiac or hepatic vagotomy had no effect. These results suggest that afferent vagus nerve originating in the upper digestive tract relays the peripheral information for suppressing LH secretion to the central nervous system during fasting.

These facts led us the following hypothesis: a neural signal emanating from the upper digestive tract during fasting reaches the medulla oblongata *via* afferent vagal nerve so as to activate the noradrenergic system projecting to the PVN, resulting in an increase in CRH release, and in turn the suppression of the LHRH and then LH release (Fig. 2). One of the promising candidates for the area relaying the vagal information to the PVN is A2 region of the nucleus of the solitary tract (NTS) in the medulla oblongata, since the region has been reported to have noradrenergic neurons projecting to the PVN and to receive the afferent vagus inputs (Ritter et al. 1992).

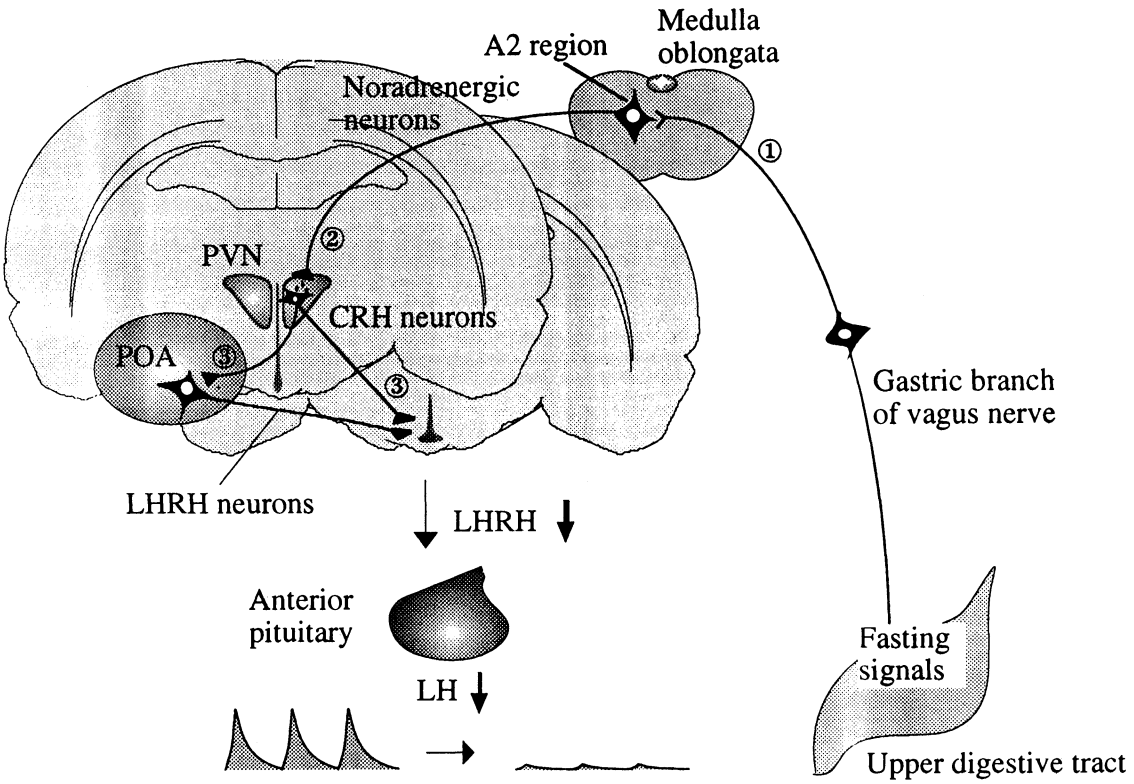

Fig. 2. Neural pathway mediating fasting-induced suppression of pulsatile LH secretion in E2-treated ovariectomized rats: 1, the information on the fasting reaches to the medulla oblongata and activates noradrenergic neurons *via* afferent gastric vagal nerves originating in the stomach or upper digestive tract; 2, norepinephrine (NE) released in the paraventricular nucleus (PVN) activates CRH neurons to release CRH; 3,CRH acts at the median eminence and/ or preoptic area (POA) to inhibit LHRH neurons. PVN, paraventricular nucleus; POA, preoptic area; CRH, corticotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone; LH, luteinizing hormone.

THE ROLE OF ESTROGEN IN ACTIVATING THE NEURAL PATHWAY ASSOCIATED WITH FASTING-INDUCED SUPPRESSION OF LH SECRETION

The above-mentioned neural pathway may be activated in the presence of estrogen but not in the absence of estrogen, since LH secretion is suppressed by 48-h fasting in intact or estradiol-primed ovariectomized rats but not in ovariectomized animals (Cagampang et al. 1990, 1991). Local estrogen implants were placed in various brain regions of ovariectomized fasted rats to determine the sites of feedback action of estrogen to activate the neural pathway mediating fasting effect (Nagatani et al. 1994). Only the animals with an estrogen implant in the PVN or A2 region showed a significant suppression of LH secretion after 48-h fasting, but the other groups of animals with an estrogen implant in the medial preoptic area (mPOA), arcuate nucleus (ARC), A1 region or locus coelureus showed no significant suppression of LH secretion after 48-h fasting. The result clearly indicates that the PVN and A2 region are the action sites of estrogen feedback to allow the 48-h fasting to suppress LH release (Fig. 3). The estrogen feedback action on the PVN and A2 in the fasted animal would be totally different from the so-called "negative feedback action" of estrogen, since estrogen implants in these two nuclei suppress LH release only during fasting but not during unfasting period. The mPOA and the ARC have been known to the sites of positive or negative feedback action of estrogen (Goodman 1978, Akema et al. 1984) for the

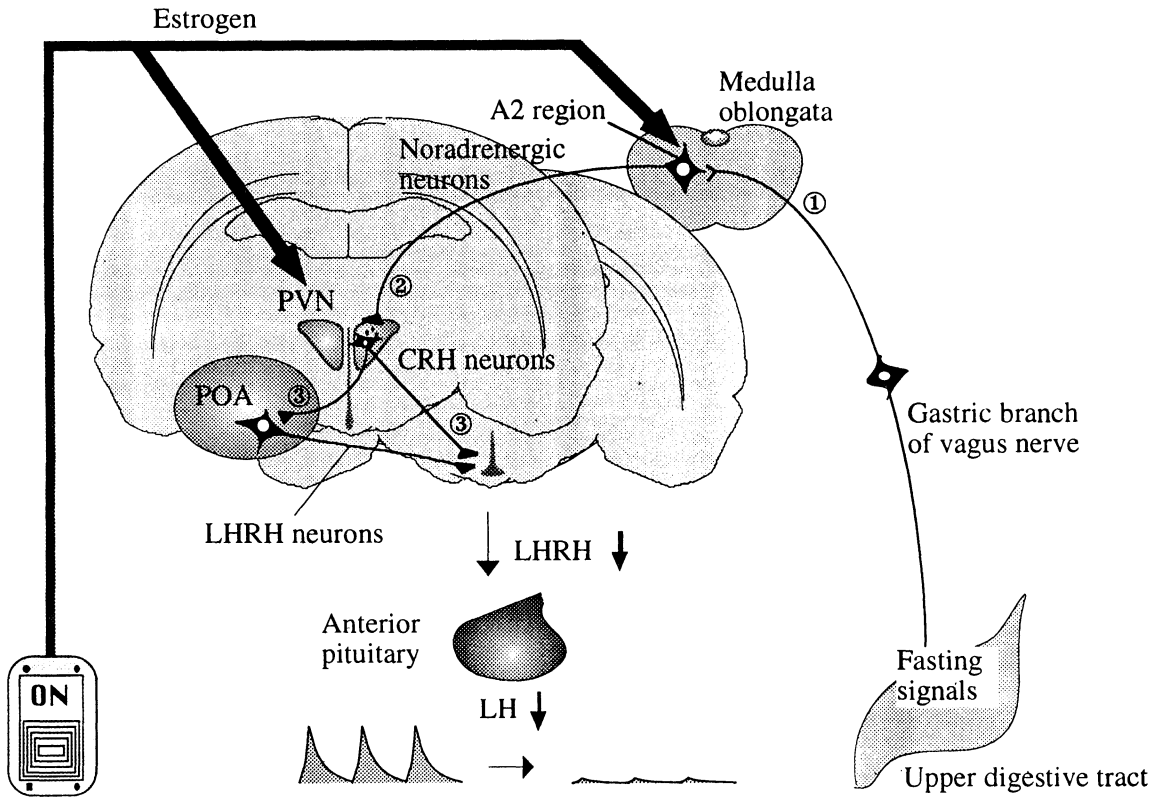

Fig. 3. Feedback sites of estrogen involved in fasting-induced suppression of pulsatile LH secretion in female rats. The feedback sites are the PVN and A2 region where the noradrenergic pathway originates in and projects to. Fasting may first induce the expression of estrogen receptors in these 2 areas. Second, estrogen bound to these receptors may regulate the activity of noradrenergic neurons in the A2 resion or sensitivity of the PVN to noradrenergic inputs from the A2 region.

brain to monitor the ovarian condition, such as follicular development. On the other hand, feedback action of estrogen in the PVN or A2 region seem to activate the neural pathway mediating the fasting--induced suppression of pulsatile LH release probably by altering the response of neurons (Fig. 4). As already mentioned, noradrenergic neurons receiving vagal afferent fibers and projecting to the PVN are located in the A2 region. It is likely that the novel estrogen feedback action we found alters the activity or action of the noradrenergic pathway from the A2 region to the PVN.

POSSIBLE MECHANISM OF ESTROGEN FEEDBACK ACTION AT THE PVN AND A2

To determine how rapidly estrogen acts on the PVN, estrogen was acutely administered into the PVN in ovariectomized 48-h fasting rats (Nagatani et al. 1996c). Perfusion of the PVN with an estrogen-containing artificial cerebrospinal fluid through a microdialysis probe suppressed pulsatile LH secretion within an hour in fasted ovariectomized rats. Interestingly, norepinephrine release in the PVN was not affected by local estrogen administration, suggesting that estrogen feedback action on the PVN may suppress pulsatile LH release without affecting local norepinephrine release in the nucleus. In addition, the estrogen feedback action on the PVN involves a rapid physiological process probably to activate CRH neurons to suppress pulsatile LH release. On the other hand, an acute administration of estrogen into the A2 region in 48-h-fasted ovariectomized rats through a microdialysis probe did not affect LH secretion or norepinephrine release in the PVN. The estrogen action at the A2 region may involve a slower process than that in the

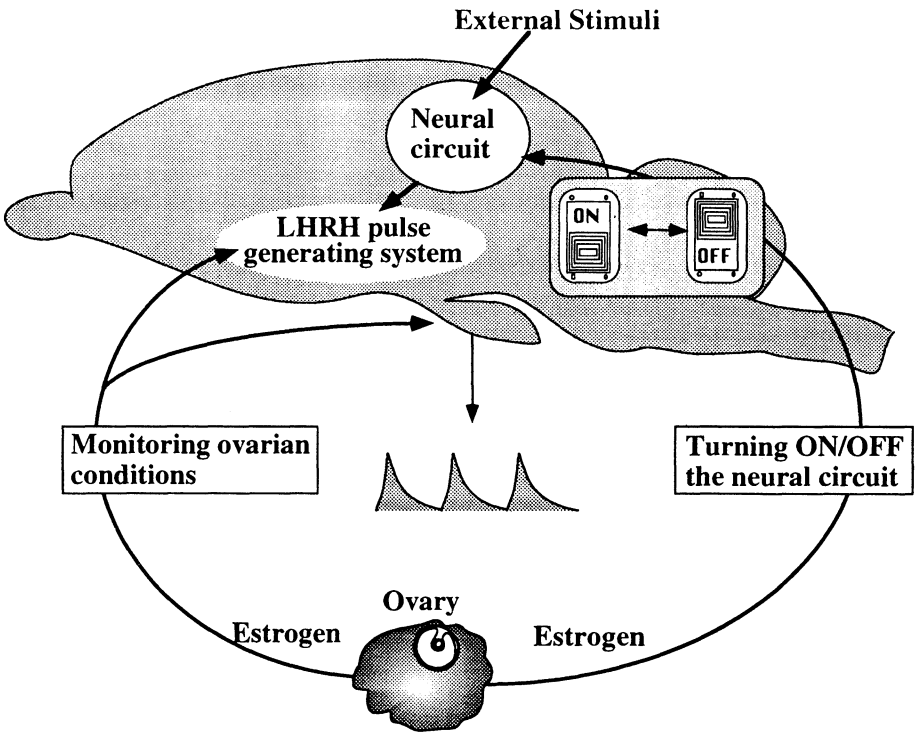

Fig. 4. Two types of estrogen feedback action on the brain to regulate the activity of hypothalamo-pituitary-gonadal axis. One is for monitoring ovarian condition and the other is for turning on the neural circuit mediating the response of gonadal axis to the external stimuli, such as stress. PVN, paraventricular nucleus; POA, preoptic area; CRH, corticotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone; LH, luteinizing hormone.

PVN. Estrogen may take a week to activate the neural mechanism in the A2 region to suppress LH secretion (Nagatani et al. 1994).

Li et al. (1994) first reported a marked increase in estrogen receptor immunoreactivity in the POA in fasted hamsters. Likewise, we have found that 48-h fasting causes a significant increase in the number of estrogen receptor-immunoreactive cells in the PVN and A2 region in ovariectomized rats (Estacio et al. 1996a). The fasting-induced estrogen receptor expression is mediated by the vagus nerve, since vagotomy abolishes the fasting-induced increase in estrogen receptor expression both in the PVN and A2 region (Estacio et al. 1996b). The increased expression of estrogen receptors in the A2 region may be directly regulated by the vagus input to the region and that in the PVN could be regulated by noradrenergic input to the PVN, which is activated by the vagus nerve, because norepinephrine is known to induce an increase in estrogen receptors in neurons in the hypothalamus in female rats (Blaustein et al. 1992, Blaustein 1993). These results strongly suggest that fasting first induces estrogen receptor expression at the beginning of the fasting and estrogen binds to these receptors to activate the neural pathway mediating fasting effect on LH secretion. Fasting may first induces an transient increase in the activity of vagus nerve and then noradrenergic pathway at the beginning of the first dark phase after the food deprivation; this activation may result in an increase in estrogen receptors in the PVN and A2 region; estrogen binding to the increased estrogen receptors may lead to an increase in the sensitivity of CRH-releasing system to the noradrenergic inputs associated with fasting. We previously found that local administration of norepinephrine into the PVN suppresses pulsatile LH release in ovariectomized E2-primed rats (Tsukamura et al. 1994). This suppression caused by a local injection of adrenaline into the PVN is mediated by CRH, since the suppression is completely blocked by icv injection of α-helical CRF. On the other hand, same norepinephrine injection into the PVN induced only a transient suppression of LH secretion in ovariectomized rats. These results suggest that estrogen modulates the response of CRH-releasing system in the PVN to noradrenergic input. In the other words, single injection of norepinephrine into the PVN induces a sustained suppression of LH secretion in estrogen-treated animals but only a transient LH

decrease in ovariectomized rats. It is possible that estrogen increases the sensitivity of the PVN by altering a neural circuit within the nucleus. It has been reported that steroidal milieu affect CRH mRNA levels in the PVN (Bohler et al. 1990, Nappi and Rivest 1995) and the promoter region of CRH gene contains the half-palindromic estrogen-responsive elements (Vamvakopoulos and Chrousos 1993). Local administration of CRH into the PVN increases both CRH and immediate-early gene mRNA levels (Parkes et al. 1993). These suggest that ovarian steroids may induce a change in the neural circuit within the PVN including an interaction between the CRH neurons themselves, resulting in CRH production. As a result, estrogen may increase the sensitivity of the PVN to the adrenergic input to ensure a sustained activation of CRH neurons and then suppression of LH secretion.

POSSIBLE NUTRITIONAL CUES REGULATING LH SECRETION DURING FASTING

Glucose availability has been considered to be a factor to be directly involved in the regulation of feeding behavior during fasted condition. Pharmacological glucoprivation by a glucose antagonist, 2-dioxyglucose (2DG), has been known to induce feeding behavior, when injected peripherally or centrally in rats (Ritter et al. 1992). The information emanating from peripheral glucose sensors located in the liver or digestive tract is transmitted to the brain *via* the vagus nerve and regulates feeding behavior (Fig.5). Glucose availability is considered to be involved in regulating gonadal activity as well (Foster and Bucholtz 1995), since peripheral 2DG injection was shown to abolish the estrous cyclicity and behavior in hamsters (Wade and Schneider 1992, Wade et al. 1996) and inhibit plasma LH levels in lambs and rats (Bucholtz et al. 1996, Nagatani et al. 1996). Blood glucose level is reduced by about 80 % in female rats after 48-h fasting when the plasma LH levels were strongly suppressed (Cagampang et al. 1990). These facts suggest that glucose availability may be one of the factors regulating LH secretion during fasting (Fig. 5). In fact, 2DG-induced suppression of LH secretion is mediated by noradrenergic input to the PVN as the fasting-induced suppression is, because 2DG-induced suppression of LH secretion is accompanied by an increase in norepinephrine release in the PVN and is blocked by local inhibition of catecholamine synthesis in the nucleus (Nagatani et al. 1996b).

Free-fatty acids or gastric distension could also be taken account into the factors involved in the regulation of LH secretion as well as feeding behavior during fasting (Ritter and Taylor 1989, Ritter et al. 1992, Wade et al. 1996). Unlike free-fatty acids or gastric distension, glucose availability could be detected by the caudal brain stem, namely the area postrema, to regulate gonadal activity (Fig. 5), because the area postrema lesion abolishes the inhibitory effect of 2DG on estrous cyclicity (Schneider and Zhu 1994), and local 2DG infusion into the 4th ventricle reduces the pulsatile LH secretion in castrated rats (Murahashi et al. 1996).

Thus, fasting induces a stress-like response of the gonadal axis and the response of gonadal axis during fasting could be due to the changes in some nutrients, such as glucose and free-fatty acids. In this context, it is speculated that malnutrition could be a kind of stress accompanied by the increase in the feeding behavior and decrease in gonadal activity. The noradrenergic pathway originating in the caudal brain stem and projecting to the PVN may be a key pathway mediating the gonadal response to stress and nutritional cues.

The rat would be just like a "plastic model" in which we could only test a simple and clear hypothesis. Physiological mechanisms in "real animals" may be much more complicated than those we described in this article. A number of mechanisms could be interacted with each other in the real animals and information derived from these interactions would be integrated to an output, LHRH a single molecule regulating whole reproductive activities. We hope that our simple model in the plastic model would contribute to the analysis of the complicated mechanisms in real animals.

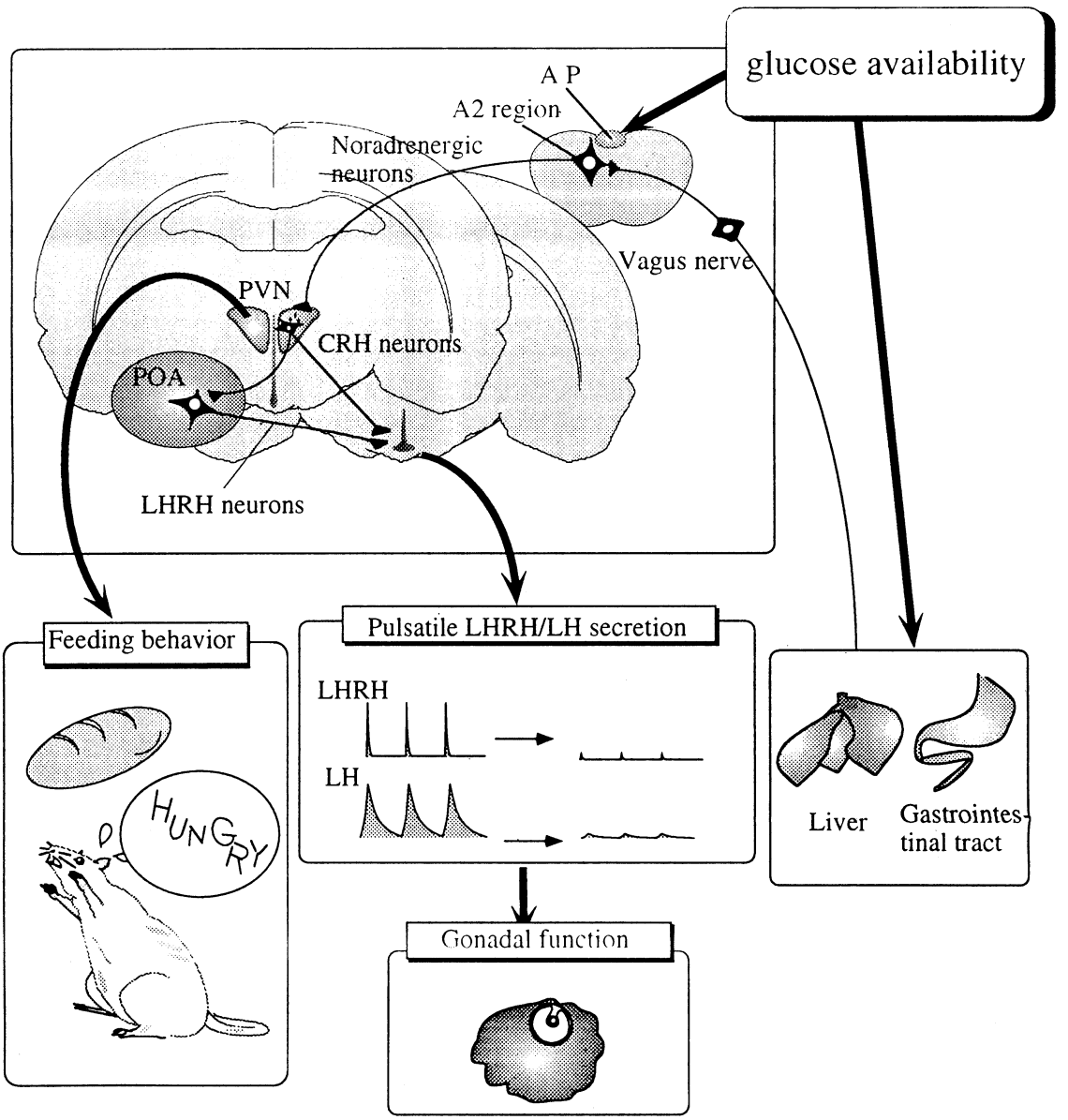

Fig. 5. Possible neuroendocrine mechanism regulating gonadal activity and feeding behavior by metabolic cues, such as glucose availability. Glucose availability could be detected by peripheral and central sensors, including the liver, digestive tract and AP, to regulate feeding behavior and gonadal functions. AP, area postrema; PVN, paraventricular nucleus; POA, preoptic area; CRH, corticotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone; LH, luteinizing hormone.

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