

## Neuropeptide Y – a neuromodulatory link between nutrition and reproduction at the central nervous system level

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### **SUMMARY**

The deficiency of nutrients in mammals' diets results in impaired gonadal function, especially in restraining of processes leading to puberty and disturbances in the course of the estrous cycle. The decreased GnRH/LH pulsatile secretion has been proposed as the most important etiological factor for nutritionally induced suppression of pituitary-ovarian functions. Although the relationship between nutrition and reproduction has been extensively investigated, little information exists about the exact mechanism connecting these two processes. One of the candidates is neuropeptide Y (NPY), synthesized in the hypothalamus. In the present paper, we reviewed the distribution of the NPY neurons, its receptors, contacts with other hypothalamic centers and its orexigenic properties. Next, we discussed the participation of NPY in the regulation of GnRH/LH secretion and underlined its dual role in the control of the reproductive system and nutritional state of organism. This information confirmed the

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hypothesis that NPY can be a candidate for a link between nutrition and reproduction at the level of the central nervous system. *Reproductive Biology* 2006 **6** Suppl. 2:21–28.

**Key words:** GnRH/LH, NPY, sheep, malnutrition

## **INTRODUCTION**

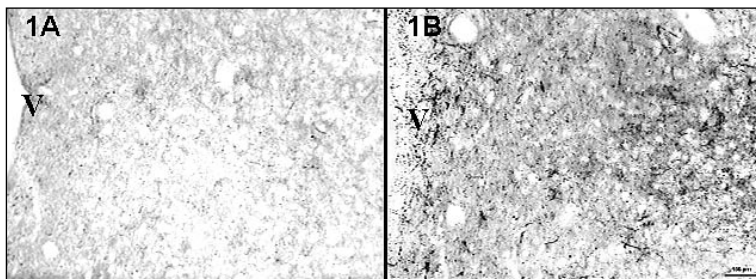
The availability of nutrition is one of the most important environmental factors necessary for the normal reproductive processes. The relationships between nutrition and reproduction in mammals mainly depend on the hypothalamo-pituitary gonadotropic endocrine system. The deficit of nutrients in many animal species causes disturbances in the secretion of gonadotropic hormones in immature as well as in adult mammals [1, 6, 11]. The decreased hypothalamic pulsatile secretion of the gonadotropic hormone-releasing hormone (GnRH), resulting in decreased luteinizing hormone (LH) synthesis and release by gonadotropic cells, has been proposed as the most important etiologic factor for the nutritionally induced suppression of pituitary-ovarian function [1, 6, 11]. Although relationships between nutrition and reproduction have been extensively investigated, there is a lack of information about the exact mechanisms connecting these two processes at the central nervous system (CNS) level. Recently, many efforts have been made to identify brain chemical factors which could generate a neuromodulatory link between the nutritional status of the organisms and reproductive hormones [18].

## **NPY AS AN OREXIGENIC FACTOR**

One of the most important, best-known and powerful orexigenic factors is neuropeptide Y [23]. This 36-amino acid peptide, a member of the pancreatic polypeptide family, is very abundant in the CNS, including hypothalamus, and in the peripheral sympathetic nervous system [32]. In the hypothalamus, NPY is synthesized primarily in perikarya of the arcuate nucleus (ARC)

and transported *via* axonal projections to the several hypothalamic nuclei involved in the regulation of appetite such as the lateral hypothalamic area, the paraventricular, dorsomedial and ventromedial nuclei [2, 3, 12]. NPY belongs to peptides binding to the seven-transmembrane-domain G-protein-coupled receptors, which are designated as  $Y_1 - Y_6$ . The  $Y_1, Y_2, Y_4,$  and  $Y_5$  receptors, cloned in the hypothalamus, have been postulated to mediate the orexigenic effects of NPY [36]. The hypothalamic level of NPY reflects the body's nutritional status, which is an essential feature for a long-term regulator of energy homeostasis. Therefore, NPY is a messenger molecule that can be considered as a physiological appetite transducer in the brain – a view supported by much evidence [15]. Central administration of NPY stimulates feeding in satiated rats and rapidly enhances behavior related to searching of food [7]. Fasting markedly augments NPY release in the paraventricular nuclei (PVN) in both *in vivo* and *in vitro* experiments [8, 12]. Long-term feeding with the protein-restricted diet in lambs increased the expression of the immunoreactive NPY in several hypothalamic nuclei (fig. 1; [24]). NPY  $Y_1$  receptor mRNA in the hypothalamus is also augmented by fasting and food restriction [37].

The NPY hypothalamic system due to its strategic distribution communicates directly with the majority of hormonal circulating signals reaching the brain. It has been known for a long time that gonadal steroids modulate food intake and body weight gain in rodents and other mammals [14]. On the other side, steroids exert a modulatory influence on NPY



*Figure 1.* Immunoreactive NPY neurons in the paraventricular nucleus of the hypothalamus of representative sheep from groups standard fed (A) and fasting for 72 hours (B). *Note:* The augmented immunoreactive staining of NPY was observed in the paraventricular nucleus in fasting animals. Scale bars, 100  $\mu\text{m}$ , V- the third ventricle of the brain.

synthesis and release [27, 28]. It has been proposed that estrogens can affect NPY synthesis in the ARC and release of the neuropeptide in the paraventricular nucleus through receptors localized on NPY neurons [5, 28]. Moreover, metabolic hormones such as insulin or leptin, can also directly affect the NPY system after crossing the blood-brain barrier [29, 38].

Neuropeptide Y together with leptin, peripheral factor synthesized by adipocytes, creates the neuro-hormonal feedback loop, which plays a crucial role in the regulation of food intake at the CNS level. The level of leptin informs the CNS about the body's energetic status. Leptin acts by receptors localized on the NPY neurons [10], causing in turn inhibition of NPY expression in the ARC [30].

### **NPY IN THE REGULATION OF GNRH/LH SYSTEM**

NPY participates in the regulation of the reproductive functions of the organism mainly controlling gonadotropic hormones secretion at the CNS level [16, 17, 21]. The specific effects of NPY on reproductive hypothalamo-pituitary axis are ambiguous and appear to depend on the species, the endocrine status and the mode (acute or chronic) of administration. Intracerebroventricular (icv) infusions of NPY in ovariectomized (OVX) rats [21], rabbits [17] or monkeys [16] resulted in the suppression of the episodic release of LH presumably through the inhibition of GnRH. In contrast, the stimulatory effect of NPY on LH release was demonstrated in OVX animals treated with ovarian steroids [13, 17]. Several studies on rats have confirmed that NPY is involved in stimulating LH secretion during the preovulatory period [13, 17]. NPY potentiates GnRH-stimulated LH secretion only in the periovulatory period, when the sensitizing action of NPY on the pituitary gland seems to be an indispensable component of the process generating LH surge [4].

The results obtained after NPY administration in the sheep are more contradictory and depend on an experimental model. NPY suppressed LH release in both OVX [20, 22] and OVX estrogen-treated sheep [22]. By contrast Porter et al. [26] failed to observe any effects of icv NPY infusions on concentration and LH pulse parameters in cycling, OVX or OVX estrogen-treated sheep. It should be pointed out here that these

contradictory data indicating different effects (stimulatory, inhibitory or no effect) of exogenous NPY on the LH secretion in sheep [22, 26] are based mainly on the measurement of LH concentration in the blood, which is insufficient to characterize the exact nature of NPY action.

Additionally, our results of the study performed on prepubertal female lambs show that icv infusions of NPY have no influence on LH concentration in the blood [34]. However, immunohistochemical and *in situ* hybridization results clearly show that exogenous NPY infused to the third ventricle of the brain increases the expression of mRNA for LH $\beta$  and the storage of LH $\beta$  subunit in gonadotropic cells of the pituitary gland. These changes suggest that in the female lambs in the prepubertal period, NPY can be involved in the synthesis and storage of LH in the pituitary gonadotrope but not in LH release [34].

The other study was performed on adult ewes being in two phases of the early anestrus period. The results have shown, that NPY was able to affect the GnRH/LH secretion in early anestrus (after the last estrous cycle), but only during a short period. NPY infused to the third ventricle of the brain stimulated GnRH release from the nerve terminals situated in the median eminence (ME) and LH release from the luteotropic cells in the pituitary gland (fig. 2). Based on these results it can be proposed that sensitivity of the GnRH/LH system to modulatory action of NPY was decreased in females with diminished sexual activity and reduced ovarian steroid blood concentration [35].

Moreover, there is morphological evidence indicating co-localization of NPY and GnRH neurons in the preoptic area and median eminence [19, 31, 33]. The part of the population of NPY terminals is located in the lateral external layer of the ME, which is a characteristic site of GnRH terminals [25]. These common neuroanatomical connections implicate physiological interactions, which can be associated with hormone release. It was demonstrated that the part of infundibular NPY neurons project to the medial preoptic area [9, 19]. NPY neurons come in close contact with GnRH neurons in the medial preoptic area and may provide direct input to both cell bodies producing GnRH in the preoptic area and to their nerve terminals in the ME [19].

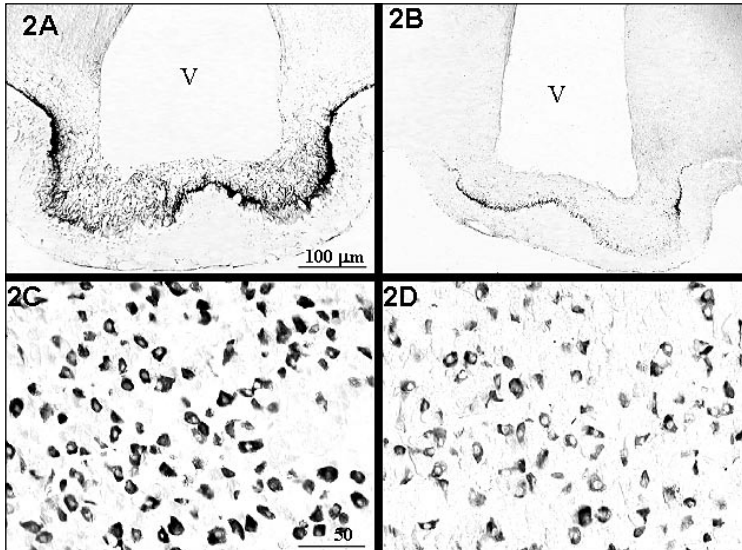


Fig.2. Immunoreactive GnRH (ir GnRH) in the median eminence of the hypothalamus (A, B) and immunoreactive LH $\beta$  (ir LH $\beta$ ) in the cells of the adenohypophyses (C, D) of two representative sheep in the early anestrus phase treated with vehicle (A, C) and NPY (B, D). *Note:* The marked decrease of the content of ir GnRH in the nerve terminals and ir LH $\beta$  in the luteotropic cells indicates higher release of both hormones after NPY infusions. Scale bars, 100  $\mu$ m, V- the third ventricle of the brain. *Reproduced with permission from [35]*

Summarizing, hypothalamic NPY neurons localized in the ARC participate in the modulation of GnRH/LH secretion in rodents, primates and sheep. The mode of NPY action seems to depend on the activity of the reproductive system. Malnutrition causes a depression of gonadotropic axis activity and simultaneously augments the secretory activity of NPY neurons. Neuropeptide Y is also known as a powerful orexigenic factor. Therefore, NPY can be considered as one of candidates for a neuromodulatory link between nutrition and reproduction at the level of the CNS.

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