

# A role of neuropeptide Y and galanin in the pituitary

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## Introduction

Many physiological functions are under both endocrine and nervous systems. The endocrine system is composed of glands that secrete hormones directly into the blood circulation to be carried towards distant target organs. In the nervous system, the hypothalamus is the control center of all autonomic regulatory activities and play a hub interconnected in brain regions including the brainstem, the limbic system, and the autonomous nervous system and also in endocrine organs. There is a bidirectional interaction between the endocrine organs and the central nervous system. The hypothalamus controls the function of the pituitary gland that is the master gland of the endocrine system. The pituitary gland is composed of anterior, intermediate, and posterior lobes. The posterior pituitary contains and releases two hormone, vasopressin and oxytocin which are synthesized in the hypothalamus. Vasopressin is an antidiuretic hormone, which retains water in the body and constricts blood vessels. The conventional function of oxytocin is contraction of the smooth muscle of the uterus and the milk ejection reflex for suckling. The anterior pituitary produces endocrine hormones containing adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), growth

hormone (GH), and prolactin (PRL). Their production and release into the blood are regulated by the hypothalamus. Each hormone regulates several physiological processes including stress, growth, reproduction and lactation in their target endocrine organs. The regulatory pathway from the hypothalamus to pituitary endocrine organs is known as hormone axis with each cascade manner. The timing of releasing the anterior pituitary hormones is adjusted to both the most favorable time in the normal physiological condition and the priority of hormone axis in abnormal events. The hypothalamic-pituitary-gonadal axis (HPG axis) in the reproduction is most sensitive in various environments. Both a physical and emotional burden on women, for example, eating disorders, depression, anxiety, stress, physical exercise, energy availability and weight loss, are associated with markedly reduced secretion of the gonadotropins in the HPG axis<sup>(1)</sup>. Increased cortisol secretion, which reflect increased endogenous CRH activity, has been noticed in eating disorders or after exercise in many women<sup>(2)</sup>. In addition to HPA hormones, vasopressin released from the hypothalamic paraventricular nucleus (PVN) is known to increase ACTH secretion in synergistical action with CRH on the corticotrophs<sup>(3)</sup>. This compensatory of increase may be effective for the adaptation to repeated stress because the stress results a down-regulation of CRH gene expression in the PVN<sup>(4)</sup>. In this case, HPA-HPG link is dependent on the hypothalamic functions. In the

relationship between fertility and energy homeostasis, studies show that severe dietary restriction, catabolic states and even short-term caloric deprivation impair fertility in mammals. Likewise, obesity is associated with infertile conditions such as polycystic ovary syndrome. These fertility involves the action of insulin and leptin in the hypothalamus<sup>(5)</sup>. The activation of HPG axis involves several neuropeptides. For an example, kisspeptin activates gonadotropin releasing hormone neurons to increase the serum levels of luteinizing<sup>(6)</sup>. In the same way, many reports refer to the modulation of the HPG axis in the hypothalamus. On the comparison, there is not so much reports about the intercellular communication in the anterior pituitary. A lot of factors that secreted within the anterior pituitary interact to synthesize and secrete the pituitary endocrine hormones. A broad survey of literature about the interaction within the anterior pituitary has been reviewed<sup>(7)</sup>. Herein, we review the action of galanin and neuropeptide Y in the pituitary and propose the galanin hypothesis in the neuronal plasticity.

### Galanin in the anterior pituitary

Galanin is a peptide consisting of a chain of 29 amino acids or 30 amino acids produced from the cleavage of a 123-amino acid length preprogalanin, which is encoded by the GAL gene. Galanin is located in the central and peripheral nervous systems and is colocalized with many neurotransmitters. Galanin is involved in the modulation of action potentials in neurotransmission. Action potentials are initiated by excitatory postsynaptic potentials from a presynaptic neuron where neurotransmitter molecules are released. While the neurotransmitters bind to their specific receptors on the postsynaptic cells, these binding open various types of ion channels. Galanin does not change the neurotransmitter binding but change the ion channel opening and/or signaling through G-protein-coupled neurotransmitter receptors.

Galanin is localized within specific cell types of the rat anterior pituitary gland. Immunohistochemical studies show that lactotrophs<sup>(8)</sup>, somatotrophs<sup>(9)</sup>, corticotroph<sup>(10)</sup> and thyrotrophs<sup>(9)</sup> contain galanin in the intact female rat. Galanin is an estrogen-inducible peptide and its gene expressed in the anterior pituitary in the control of physiologic levels of circulating estrogen<sup>(11,12)</sup>. Since

the production and secretion of galanin in the anterior pituitary are stimulated by estrogen, the interaction between galanin and pituitary endocrines may be involved in the period of the exposure of estrogen in the homeostasis. Estrogen is the primary female sex hormone which is responsible for the development and regulation of the female reproductive system. The release of estrogen is dependent on the estrus cycle of each vertebrate. The estrogen concentration in the circulation is the highest level in the proestrus state, wherein LH surge is stimulated. However, there is little knowledge of the direct interaction between galanin and the production of LH. Moreover, both galanin knockout and overexpressing mice show the failure of infertility phenotypes. Therefore, the present studies demonstrate no relationship between galanin and gonadotrophs in the pituitary.

### Interaction between galanin and endocrine cells in the pituitary

In the consideration of the physiological actions, we should regard that estrogen in physiological and pharmacological doses produces a significant increase in galanin content. Targeted disruption of the murine galanin gene shows that PRL mRNA levels and protein content of adult female were reduced by 30-40% compared with wild-type controls<sup>(13)</sup>. Mice targeted overexpression of galanin by using rat PRL promoter shows that PRL mRNA levels were increased in female transgenic mice<sup>(14)</sup>. These evidences convince us that galanin in the pituitary promotes the synthesis of PRL with the control of estrogen. On the somatotrophs, galanin progresses GH release under the induction of growth hormone-releasing hormone (GHRH) and its release is completely inhibited by somatostatin infusion<sup>(15)</sup>. Pituitary GHRH receptor mRNA levels is increased by ovariectomy and decreased by estrogen. GH mRNA levels were unchanged by ovariectomy but decreased after estrogen treatment<sup>(16)</sup>. Galanin is expressed in the mammalian anterior pituitary as mRNA<sup>(11,17-19)</sup> and protein<sup>(20)</sup>. Therefore, galanin to somatotrophs has an enhancing action of GH release.

Immunohistochemistry on pituitary tissues shows that galanin and ACTH were coexpressed in the cytoplasm of the same adenoma cells in the corticotrophs<sup>(10)</sup>. In this study, Crooke's cells and basophilic cells spreading to the

posterior lobe were positive for galanin. An intravenous bolus injection of galanin does not alter baseline and releasing hormone-stimulated secretions of PRL, TSH, LH, and FSH, but to reduce slightly in both the ACTH and cortisol in the stimulation of CRH<sup>(21,22)</sup>. GAL is involved in a small partial inhibition of the preovulatory surges of LH without altering the FSH surge<sup>(23)</sup>. Collectively, galanin affects the reduced secretion of ACTH and the increased secretion of PRL and GH. In these interaction, no correlations exist between GAL and either GH or ACTH circadian profiles<sup>(24)</sup>.

Since the lack of rhythmicity in the circadian profile of plasma GAL levels in healthy human subjects, physiologically circulating levels of GAL are likely not involved in the regulation of GH secretion<sup>(24)</sup>. Locally produced galanin inhibits ACTH release by modulation of corticotropin release<sup>(25,26)</sup>. Over-expression of galanin in the anterior pituitary using the rat GH promoter influences to promote the differentiation of lactotrophs and to increase PRL, GH, galanin but not TSH and LH in serum levels<sup>(27)</sup>. Since galanin and ACTH are coexpressed in the cytoplasm of the same adenoma cells, the interaction between galanin and proopiomelanocortin (POMC) may occur in the same cells. Both galanin and galanin mRNA are dramatically up-regulated in the anterior pituitary by estrogen, which is released at the early proestrus state<sup>(12,28)</sup>. Proteolytic processing of POMC release ACTH and is mediated through either PC1 or PC2, when secretory granules become mature. Cathepsin L generates peptide intermediates with N-terminal basic residue extensions<sup>(29,30)</sup>. The traffic of the processing and secretory granule formation is complicated in the same cells, but it is possible that the formation of galanin and ACTH granules are shared with the same secretory and transportable machine. As far as the corticotrophs, the inhibition of the preovulatory surges of LH by galanin may be included in the reduced secretion of ACTH.

LH surge is responsible for initiating ovulation and results from an abrupt and massive increase in hypophyseal portal GnRH. Estrogen influences upon the GnRH neurons and pituitary gonadotrophs to generate the preovulatory LH surge. Although the surge of GnRH occurs between proestrus 1200 h and proestrus 1800 h, the expression of galanin in the hypothalamus is constant in the state of proestrus 1200 h, proestrus 1800 h, and estrus 1800 h in situ hybridization<sup>(31)</sup>. A part

of the galanin mRNA is located in the GnRH neurons and is the maximum peak of the galanin mRNA in the estrus state. The expression of galanin in the hypothalamus is not associated to GnRH surge but to basic level of GnRH, known as GnRH pulse generator.

Many studies support that estrogen exerts a powerful stimulatory influence on GnRH secreted from nerve terminals in the median eminence to initiate the LH surge. However, it remains in both positive and negative feedback pathways whether estrogen acts directly to GnRH neurons in the hypothalamus or not<sup>(32)</sup>. The interaction between galanin and LH surge in the pituitary remains unknown although galanin and galanin mRNA are dramatically up-regulated in the anterior pituitary by estrogen.

### The endocrine galanin hypothesis

We here hypothesis that the serum level of galanin determines the modulation of nociception and harmonizes the sensitivity to threshold of nociception in the peripheral nervous system. This hypothesis is deduced from the followings.

The preprogalanin mRNA expression in the pituitary is enough amount of an endocrine hormone. Its corresponding amount of the galanin receptors are not present in the pituitary. If the galanin produced in the pituitary is an endocrine hormone, the galanin must play a role in the peripherals. The periodic rhythm of galanin is the exactly same as that of ovulation or LH surge because the expression of galanin is dramatically up-regulated in the anterior pituitary by estrogen. If galanin harmonizes the sensitivity to threshold of nociception in the peripheral nervous system, the periodic rhythm of galanin requests to standardize the sensitivity by galanin periodically.

Plasma galanin levels in postmenopausal women are significantly lower than in young women<sup>(33)</sup>. Climacteric patients with nervousness have lower serum galanin concentration than patients without this symptom<sup>(34)</sup>. Although the symptoms of menopausal women include vasomotor symptoms, urogenital atrophy, osteoporosis, cardiovascular disease, cancer, psychiatric symptoms, cognitive decline, and sexual problems, vasomotor symptoms in the peripheral nervous system are independent of any significant change in mood or anxiety symptoms of the central system on the therapies.

An infusion of galanin is a dose-dependent increase of galanin in the circulation and induces the release of GH and PRL, and cardiovascular effects<sup>(35)</sup>. This means the circulation of galanin is effective to both the central nervous system and the peripheral nervous system.

Galanin knockout mice reveal nociceptive deficits following peripheral nerve injury<sup>(36)</sup>. Galanin over-expressing animals show that galanin is an inhibitory neuromodulator of spinal cord transmission<sup>(37)</sup>. Galanin plays a significant role of peripheral galanin in pain transmission. The galanin levels in the circulation modulate the neurotransmitter release of acetylcholine, serotonin, norepinephrine, and neuropeptides. The neuromodulation of galanin may cause by decreasing the sensitivity of neurotransmitters rather than by inhibiting the neurotransmitter actions.

The serum level of galanin is largely influenced in the same events by individual differences, age, gender, and diseases. According to the hypothesis, the threshold of sensitivity in the neurotransmission is diversified by galanin levels, which presents to form the neuronal plasticity in the adaptation.

### Interaction between neuropeptide Y and gonadotrophs in the anterior pituitary

Neuropeptide Y (NPY) containing 36 amino acids is an abundant and widespread peptide in the mammalian nervous system which acts as a neurotransmitter<sup>(38)</sup>. NPY is discovered in pituitary portal blood of rats. Since immunocytochemistry demonstrates that the endogenous NPY presents in gonadotrophs, somatotrophs, corticotrophs and some lactotrophs, but not in thyrotrophs, NPY was indicated to play a direct regulatory role in adenohipophyseal secretion<sup>(39)</sup>. In fact, the concentration of NPY immunoreactivity in portal plasma ( $52.0 \pm 4.0$  ng/ml, mean  $\pm$  SEM) was three times greater ( $p < 0.005$ ) than in systemic plasma ( $16 \pm 4.5$  ng/ml)<sup>(40)</sup>. Both intravenous ( $300 \mu$ g) or intraventricular ( $2$  to  $15 \mu$ g) injection of NPY provide a significant and long-lasting decrease of plasma LH levels in gonadectomized male rats<sup>(41)</sup>. NPY produces no significant change in release of pituitary hormones in anterior pituitary cells in culture<sup>(41)</sup>. These mean that NPY is released into the hypophyseal portal blood for transportation to the anterior pituitary where it enhances the release of LH in response to GnRH. Finally,

the function of NPY in the pituitary involves an allosteric increase in GnRH binding to its receptor leading to augmented influx of  $Ca^{2+}$  from the extracellular space. NPY plays a critical role in stimulating the basal pattern of luteinizing hormone (LH) release as well as the preovulatory surge of LH release in several species. The stimulatory effect of NPY on LH secretion is dependent upon the presence of gonadal hormones<sup>(42)</sup>. Genetic modification also supports the stimulation of LH secretion by NPY. NPY knockout mice show the attenuation of LH surges<sup>(43)</sup>.

### Conclusion

We propose the hypothesis that galanin produced mainly in the pituitary determines the modulation of nociception as an endocrine hormone and harmonizes the sensitivity to threshold of nociception in the peripheral nervous system.

The key neuroendocrine signals for stimulation of gonadotropin surges have been known for many decades, and the cellular mechanisms that integrate these signals have been studying. In this review, we focused on the interaction between LH release and its related peptides in the pituitary tissue. NPY plays an important role of enhancing LH release in the proestrus LH surge at the pituitary portal vessels. The interaction between NPY and GnRH on GnRH receptors will provide a potential target for the treatment of ovulatory disorders.

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