

## Galanin modulates pituitary hormones release

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### Abstract

**OBJECTIVES:** Galanin and its receptors are widely distributed within the central and peripheral nervous system, especially in hypothalamus including preoptic area, paraventricular nucleus (PVN), supraoptic nucleus (SON) and median eminence. Galanin plays an important role in the control of food intake, energy expenditure, reproduction, water balance and various neuroendocrine functions. Galanin may affect hormones release, but the exact mechanism of the peptide action remains unclear and possible direct effects of galanin on the pituitary are controversial. The aim of this study was to examine the effects of galanin on pituitary hormones release after the central and peripheral administration of the peptide.

**MATERIAL AND METHODS:** (i) *Experiment I – Intracerebroventricular (icv) administration of galanin:* Galanin at a concentration of 0.5 µg in 5µl vehicle (artificial cerebrospinal fluid) or equal volume of the vehicle was slowly (1µl/min) infused into the third ventricle with an automatic pump (CMA/100; Sweden) through an inner cannula inserted into the guide cannula. After the end of the infusion the rats were transferred to their home cages with free access to food and water. At 60 min after the infusion of galanin or vehicle, animals were decapitated and trunk blood was collected in plastic tubes containing 1000 IU aprotinin (inhibitor of protease) per each ml of blood. (ii) *Experiment II – Intravenous (iv) injection of galanin:* Galanin in a dose of 10 µg in 300 µl of saline or 300 µl of saline alone was injected into the tail vein. After the injection the animals were transferred to individual cages with free access to food and water. At 60 min after the injection of galanin or saline, animals were decapitated, and trunk blood was collected in plastic tubes containing 1000 IU of aprotinin (Trascolan). The blood samples were centrifuged (3000 rpm for 20 min at 4°C). Serum samples were frozen until hormonal analyses were performed. Serum rLH, rFSH, rPRL, rGH, rTSH concentrations were measured with RIA methods.

**RESULTS:** Galanin administered icv increased significantly rPRL and rTSH levels ( $p < 0.01$ ,  $p < 0.05$ , respectively). Plasma rPRL and rTSH concentrations were not changed after iv injection of galanin. Galanin injected centrally inhibited significantly rGH release ( $p < 0.01$ ), however, galanin given iv stimulated rGH ( $p < 0.01$ ). Serum rLH and rFSH concentrations were not changed after icv and iv injections of galanin.

**CONCLUSION:** Galanin may be involved in the modulating mechanism of pituitary hormones release.

## Introduction

Galanin is a 29 to a 30-amino-acid peptide, initially isolated from the small intestine of the pig [1, 2].

Galanin and its receptors are widely distributed within the central and peripheral nervous system, especially in hypothalamus including preoptic area, paraventricular nucleus (PVN), supraoptic nucleus (SON) and median eminence [3]. Galanin is also present in the respiratory and genitourinary tracts [4, 5] and in the liver, pancreas, thyroid gland, adrenal medulla, eye, skin and muscle [6, 7].

Receptors for galanin are the G protein – coupled class, forming three distinct subtypes, GalR1, GalR2 and GalR3 [8].

Galanin plays an important role in the control of food intake, energy expenditure, reproduction, water balance and various neuroendocrine functions [9, 10].

It has been demonstrated that centrally injected galanin stimulates food intake, especially the consumption of fat and carbohydrate as well as inhibits energy expenditure and sympathetic nervous system activity [9, 10, 11, 12].

Galanin is colocalized with other neuropeptides such as corticotrophin releasing factor (CRF), thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), growth hormone releasing hormone (GHRH), vasopressin (AVP) and oxytocin (OT) [13, 14, 15, 16, 17, 18, 19].

Galanin is found in high concentrations in hypothalamus and this peptide is secreted into hypophysial portal blood [20, 21, 22].

Galanin may affect hormones release, but the exact mechanism of the peptide action remains unclear and possible direct effects of galanin on the pituitary are controversial [23, 24, 25, 26, 27].

The aim of this study was to examine the effects of galanin on pituitary hormones release after the central and peripheral administration of the peptide.

## Material and Methods

### *Animals and surgery*

Female ovariectomized (OVX) Wistar-Kyoto rats (240–260g) were maintained under controlled conditions (14L: 10D, lights on at 06.00h, temperature at 23 ± 1°C) with free access to food and water. All experimental procedures were approved by the First Warsaw Ethic Committee for Experiments on Animals (the M. Nencki Institute of Experimental Biology, the Polish Academy of Science).

### *Experiment I. Intracerebroventricular (icv) administration of galanin*

The animals were anesthetized ip with ketamine and implanted with a stainless-steel guide cannula, 23 gauge cannula was located in the third cerebroventricle (0.8 mm posterior and 7.0 mm ventral to the bergma at the midline) according to the atlas of Paxinos and Watson [28]. The inside of the cannula was closed by a remov-

able stainless-steel plug. The placement of the intracerebroventricular cannula was verified by an injection of methylene blue dye after decapitation. The brain was inspected for complete spread of the dye in the third ventricle. Data from any subject with inadequate spread of the marker were discarded.

After the surgery, the rats were transferred to individual cages with food and water freely available. During a 7-day period of recovery, rats were handled daily to minimize any stress associated with handling on the day of the experiment.

On the day of the experiment, 2 h before galanin administration, a stainless-steel guide cannula was opened and controlled its patency. Intracerebroventricular infusion of galanin (rat) (Bachem), was performed to freely moving rats. Galanin at a concentration of 0.5 µg in 5µl vehicle (artificial cerebrospinal fluid) or equal volume of the vehicle was slowly (1µl/min) infused into the third ventricle with an automatic pump (CMA/100; Sweden) through an inner cannula inserted into the guide cannula. After the end of the infusion the rats were transferred to their home cages with free access to food and water. At 60 min after the infusion of galanin or vehicle, animals were decapitated and trunk blood was collected in plastic tubes containing 1000 IU aprotinin (inhibitor of protease) per each ml of blood. The time-span from removal of the animals from their cages to decapitation was approximately 2 min.

### *Experiment II-Intravenous (iv) injection of galanin*

Galanin in a dose of 10 µg in 300 µl of saline or 300 µl of saline alone was injected into the tail vein. After the injection the animals were transferred to individual cages with free access to food and water. At 60 min after the injection of galanin or saline, animals were decapitated, and trunk blood was collected in plastic tubes containing 1000 IU of aprotinin (Trascolan).

The blood samples were centrifuged (3000 rpm for 20 min at 4 °C). Serum samples were frozen until hormonal analyses were performed.

### *The hormone measurement*

Serum concentrations of rLH, rFSH and rPRL were measured by RIA in duplicates using reagents prepared by Dr. A.F. Parlow and provided by the NIDDK (Bethesda, MD). Values were expressed in terms of the LH-RP3, FSH-RP2 and PRL-RP3 of reference standard, respectively.

Serum concentrations of the rTSH and rGH were measured by kits provided by Biocode S.A., France. The limit of detection for TSH was 0.1 ng/ml and 1 ng/ml for GH. All measurements were made in one assay. Intra-assay for all hormones were: LH – 6.5%, FSH 6.7 %, PRL – 6.0%, GH – 6.8, TSH – 6.0 %.

Since we found substantial amount of variation between the controls at the various time points, the responses of hormones to galanin were compared to the common control (mean of all controls).

The statistical analysis was performed with unpaired t-test and one-way ANOVA as appropriate p<0.05 was considered significant.

**Table 1:** Effects of galanin injected intracerebroventricularly (icv) and intravenously (iv) on pituitary hormones release in ovariectomized (ovx) female rats

| HORMONES   | CONTROL icv | icv GALANIN              | CONTROL iv | iv GALANIN                |
|------------|-------------|--------------------------|------------|---------------------------|
| rLH ng/ml  | 5.4 ± 0.3   | 5.5 ± 0.6<br>n.s         | 4.3 ± 0.4  | 4.7 ± 0.5<br>n.s          |
| rFSH ng/ml | 7.9 ± 1.0   | 6.1 ± 0.9                | 23.2 ± 0.9 | 20.1 ± 1.1                |
| rPRL ng/ml | 1.7 ± 0.2   | ↑ 3.0 ± 0.5<br>(p<0.01)  | 0.8 ± 0.07 | 1.0 ± 0.1<br>n.s          |
| rTSH ng/ml | 3.2 ± 0.2   | ↑ 4.4 ± 0.5<br>(p<0.05)  | 3.5 ± 0.2  | 3.8 ± 0.2<br>n.s          |
| rGH ng/ml  | 27.3 ± 4.0  | ↓ 14.4 ± 2.7<br>(p<0.01) | 35.2 ± 5.0 | ↑ 54.9 ± 15.0<br>(p<0.01) |

## Results

Effects of galanin injected intraventricularly (icv) and intravenously (iv) on pituitary hormones release in OVX female rats were presented in *Table 1*.

Galanin administered icv increased significantly rPRL and rTSH levels (p<0.01, p<0.05, respectively). Plasma rPRL and rTSH concentrations were not changed after iv injection of galanin. Galanin injected centrally inhibited significantly rGH release (p<0.01), however, galanin given iv stimulated rGH (p<0.01).

Serum rLH and rFSH concentrations were not changed after icv and iv injections of galanin.

## Discussion

It has been reported that galanin may play an important role in the regulation of the hypothalamic-pituitary-gonadal axis and the somatotrophic axis, because galanin is coexpressed in a subset of gonadotropin-releasing hormone (GnRH) and growth hormone-releasing hormone (GHRH) neurons in the brain. [29, 30]. The coexistence of GnRH and galanin in preoptic area was demonstrated by Coen et al. [31]. Galanin stimulates the release of GnRH *in vitro* from isolated arcuate nucleus-median eminence fragments [32].

Injection of galanin into the third cerebral ventricle (icv) leads to an increase of LH release in ovariectomized (ovx) or steroid-primed female rats [33] and the galanin receptor antagonist – galantide inhibits basal LH and LH surge in steroid primed OVX rats [34]. Galanin mRNA in the pituitary is increased following the estrogen treatment, and galanin concentrations are decreased in OVX rats [35, 36, 37]. Galanin administered to the medium of dispersed pituitary cells induces a dose-dependent increase in the LH content and exaggerates the stimulation of LH secretion by GnRH [38].

We did not observe significant changes in LH and FSH release after the central (icv) and intravenous (iv) injections of galanin in ovariectomized rats (OVX).

It has been published that ovariectomy reduces the number of GnRH neurons [39] and the estradiol treatment reverses an expression of galanin [40].

Gajewska et al. [41] demonstrated that icv pulsatile injections of galanin increased  $\alpha$  and LH  $\beta$  mRNA contents in the pituitary gland and those effects were oestrogen/progesterone-dependent. The authors suggested that the stimulatory effects of galanin on LH secretion and gene expression might be mediated through the modulation of GnRH.

Endogenous ligand for galanin receptors and galanin-like peptide (GALP) and its mRNA have been localised in cells of the hypothalamic nuclei (Arc), median eminence and neurohypophysis [42, 43]. Galanin-like peptide (GALP) is a 60-amino acid neuropeptide recently isolated from the porcine hypothalamus and it is able to activate galanin receptors [44]. In addition to POMC/CART and NPY/AgRP neurons, GALP neurons may also play a role in the metabolic and behavioural response to leptin [45].

The injection of GALP directly into the cerebral ventricles causes changes in food intake and stimulates LH release in animals [46, 47, 48]. GALP is regulated by leptin and this observation suggests that GALP may integrate information between the metabolic status and the reproductive axis [49]. Mathew et al. [49] postulated that an increase of LH release in response to GALP in the male rhesus macaque was mediated through GnRH-dependent mechanism. Splett et al. [50] demonstrated that galanin enhanced GnRH-stimulated LH secretion in the presence of high levels of estrogen in OVX animals. Cunningham [51] observed that central injection of GALP increased food intake and suppressed the thyroid axis.

In our study galanin administered icv increased TSH release. However, we did not observe significant changes in TSH release after iv injection of galanin.

In our previous experiments “*in vitro*” galanin did not stimulate TSH release from cultured pituitary cells [52].

Galanin also plays an important role in the regulation of somatotrophic axis. The injection of galanin induces the release of GH in rats and humans [26, 27, 53, 54] and galanin antiserum inhibits GH release [27].

Incubation of median eminence fragments with galanin leads to an increase of GHRH concentration in the medium [55]. Growth hormone (GH) release in response to GH-releasing hormone in humans is

enhanced by galanin [56]. The blunted response of GH to GH-RH in elderly men appears to normalize after the galanin treatment [57]. Antisera to GHRH inhibit the galanin-induced stimulation of GH in rats [58]. The results may suggest that galanin stimulates GH via GHRH.

Our results demonstrate that galanin given intravenously (iv) stimulated significantly GH release.

However, icv injection of galanin inhibited GH release. This finding is difficult to explain. In future we are going to do experiments with higher doses of galanin injected icv. Our previous studies [52] revealed direct stimulating effects of galanin on GH release from pituitary cells in the cell culture.

The direct effects of galanin on the pituitary are also controversial. Some authors observed stimulatory effects [23, 24, 52] and others [25] showed inhibitory direct effects of galanin on GH release.

We found that galanin administered icv increased significantly prolactin release but stimulating effects were not observed after iv injection, as well as in experiments *in vitro*.

De Marinis et al. [54] observed that iv injection of galanin in patients with anorexia nervosa stimulated GH and PRL release.

It could be speculated that the discrepancies and opposite results observed after icv and iv injection may be the result of a cooperation of galanin with other neuropeptides involved in the mechanism of pituitary hormones release.

## Conclusions

Galanin may be involved in the modulating mechanism of pituitary hormones release.

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