Galanin in the regulation of the hypothalamic-pituitary-adrenal axis (Review)

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Abstract. Galanin is a regulatory 30- or 29-amino acid peptide, widely distributed in the nervous system and gut, that acts via three subtypes of G protein-coupled receptors, named GAL-R1, GAL-R2 and GAL-R3. Findings have been accumulated that galanin regulates neuroendocrine hypothalamic axes, including the hypothalamic-pituitary-adrenal (HPA) one. Galanin and its receptors are expressed in the hypothalamic paraventricular and supraoptic nuclei, anterior pituitary and adrenal medulla. Adrenal cortex does not express galanin, but is provided with GAL-R1 and GAL-R2. The bulk of evidence indicates that galanin stimulates the activity of the central branch of the HPA axis (i.e. the release of corticotropin-releasing hormone and ACTH), thereby enhancing glucocorticoid secretion from the adrenal cortex. Investigations carried out in the rat show that galanin is also able to directly stimulate corticosterone (glucocorticoid) secretion from adrenocortical cells, through GAL-R1 and GAL-R2 coupled to the adenylate cyclase-protein kinase A signaling cascade, and nor-epinephrine release from adrenal medulla. There is indication that galanin may also enhance corticosterone release via an indirect paracrine mechanism involving the local release of catecholamines, which in turn activate ß-adrenoceptors located on adrenocortical cells. The physiological relevance in the rat of the glucocorticoid secretagogue action of galanin is suggested by the demonstration that the blockade of galanin system significantly lowers basal corticosterone secretion. There is also evidence that galanin plays a role in the modulation of HPA-axis response to stress, as well as in the pathogenesis of pituitary adenomas and perhaps of pheochromocytomas.

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1. Introduction

Galanin is a regulatory peptide (30- and 29-amino acid residues in humans and other mammals, respectively) first isolated from the pig intestine in the late 80s (1). It was named galanin because in the pig it possesses an N-terminal Glycine (position 1) and a C-terminal amidated Alanine (position 29). Galanin is widely distributed in the body tissues and organs, such as the central nervous system and gut, and regulates several biological processes, including neuroendocrine hypothalamic activity and food intake (reviewed in refs. 2-5).

Evidence has been accumulated that numerous neuropeptides involved in the central regulation of feeding (e.g. neuropeptide-Y, leptin, orexins, cholecystokinin, neuropeptide-W and beacon) control the hypothalamic-pituitary-adrenal (HPA) axis, acting on both its central (6-14 and refs. therein) and peripheral branch (13,15-28 and refs. therein). The interactions of peptides regulating food intake with the HPA axis are of great relevance, because adrenal glucocorticoid hormones are known to be involved in the positive control of energy homeostasis and adipogenesis (29,30).

Findings indicate that galanin may be included in this group of regulatory peptides, but, despite the quite large mass of investigations, only a short survey of the role of galanin in the regulation of the HPA axis has been published (31). Thus, after a short account on the biology of the galanin system, we will herein review data indicating that galanin and its receptors are expressed in all the anatomical components of the HPA axis, and galanin is involved in the functional regulation of HPA axis under both physiological and pathological conditions.

2. Biology of galanin and its receptors

Galanin. Human galanin gene is located on chromosome 11q13.3-q13.5, and consists of 6 exons and 5 introns. Exons 2-5 encode prepro-galanin peptide, whose post-translational cleavage gives rise in a stochiometric 1:1 ratio to galanin and

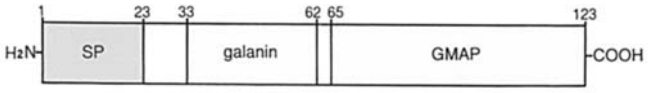

Figure 1. Scheme illustrating the structure of human prepro-galanin, and the location of galanin and GMAP. SP, signaling peptide.

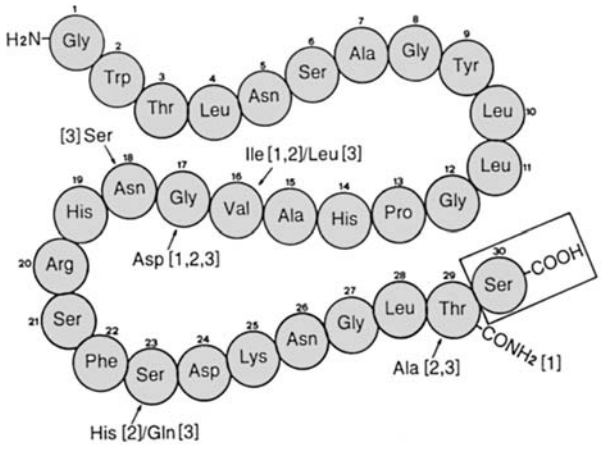

Figure 2. Amino-acid sequence of human galanin (1-30 sequence) and non-human galanin (1-29 sequence). Amino-acid substitutions in rats [1], pigs [2] and cows [3] are indicated by arrows.

galanin mRNA associated peptide (GMAP) (Fig. 1). Galanin consists of 30-amino acid residues in humans, and 29-amino acid residues in other species so far examined. The 1-15 N-terminal sequence is fully conserved, while the C-terminal portion displays greater variability. The C-terminus is amidated in all 1-29 sequences, while in humans the presence of Ser in 30 position prevents amidation (Fig. 2). Galanin is widely distributed in the central and peripheral nervous system, where it acts as a neurotransmitter/neuromodulator: its physiological functions include regulation of feeding, memory, neuroendocrine axes, nociception and nerve regeneration. Galanin is also present in the gut, where it modulates insulin release and intestine contractility. GMAP function has been less extensively investigated, but there is evidence that it may be involved in spinal-cord transmission (3-5).

Galanin receptors and their signaling mechanisms. The biological activity of galanin, probably associated to its N-terminal fully conserved sequence, occurs via the activation of three G protein-coupled receptor subtypes, that have been cloned and pharmacologically characterized: GAL-R_1, GAL-R_2 and GAL-R_3. Galanin-receptor distribution reflects that of galanin, although there is indication that GAL-R_3 expression is less abundant than that of the other two subtypes. Galanin-receptor activation involves different signaling pathways (Fig. 3). GAL-R_1 and GAL-R_3 inhibit adenylate cyclase (AC) and activate inward K^+ currents via pertussis toxin-sensitive $G_{i/o}$ protein, while GAL-R_2 predominantly activates phospholipase-C (PLC)/protein kinase (PK)-C and inositol-3-phosphate (IP_3) cascade via a pertussis toxin-insensitive $G_{q/11}$ protein. However, GAL-R_2 is thought to signal also via $G_{i/o}$ proteins (32-35; and reviewed in refs. 4,5,36).

3. Expression of galanin and its receptors in the HPA axis

Hypothalamus. Immunocytochemistry (ICC) showed that galanin is co-expressed with arginin-vasopressin (AVP) and corticotropin-releasing hormone (CRH) in the hypothamic paraventricular nucleus (PVN) (5,37,38), and with AVP and oxytocin (OT) in the magnocellular neurons of the supraoptic nucleus (SON) (39-45). The expression of galanin, AVP and OT in the rat SON was shown to be modulated by various physiological stimuli, among which osmotic ones (46,47). The magnocellular SON neurons are provided with nor-adrenergic innervation, and nor-adrenergic system was found to activate these AVP- and OT-expressing neurons (48). Recent findings indicated that in the rat SON nor-adrenergic system also up-regulates galanin expression (49).

Galanin-receptor expression has been detected in the rat hypothalamus, its level being GAL-R_1>GAL-R_2>GAL-R_3 (35,50). ICC demonstated GAL-R_1 immunoreactivity (IR) in the rat and sheep PVN and SON (47,51-54). Osmotic stimuli have been reported to up-regulate GAL-R_1 expression in the rat SON (55), and this observation, coupled to the above mentioned findings (49), suggests that galanin may be involved in the autocrine-paracrine control of AVP secretion.

Pituitary gland. Abundant evidence indicates that galanin is expressed in the mammalian anterior pituitary as mRNA and protein (56-61). *In situ* hybridization and ICC showed that galanin-positive cells are: i) in female rats predominantly lactotrophs (62-65), where galanin is co-localized with prolactin in the secretory granules (66); ii) in male rats mainly somatotrophs, thyreotrophs (61) and corticotrophs (65,67); iii) in adult male monkeys thyreotrophs and gonadotrophs (68); and iv) in normal human pituitary and pituitary adenomas almost exclusively corticotrophs (69,70). Galanin-positive nerve fibers were found in the dog, monkey and human anterior pituitary (71,72).

The presence of high-affinity galanin binding sites has been detected in the rat anterior pituitary (73), and subsequent studies evidenced the expression, as mRNA and protein, of GAL-R_2 and GAL-R_3, but not GAL-R_1 (35). No ICC investigations have been carried out to ascertain the cellular localization of such receptors.

Adrenal gland. Although earlier studies did not detect galanin mRNA in the rat adrenals (74), subsequent investigations demonstrated it in adrenal medulla not only of rats (75-77), but also of cows (78-80) and pigs (57,81). Evidence has been provided that galanin gene transcription is enhanced i) by Ca^{2+} influx and activation of PKA and PKC in bovine chromaffin cells, its promoter possessing both TPA- and cyclic-AMP (cAMP)-responsive elements (79,80); and ii) in the rat adrenal medulla by surgical or chemical interruption of splanchnic-nerve transmission (75). No galanin mRNA expression was found in the rat adrenal cortex (77). Radioimmune assay (RIA) demonstrated sizeable galanin-IR concentrations in the adrenal medulla of humans (82,83), pigs and cats (57,79,84,85), rabbits (86,87) and rats (77,88,89), where its concentration increases after hypoglycemic shock (88), as well as in human pheochromocytomas (82). Galanin-IR release from perfused pig

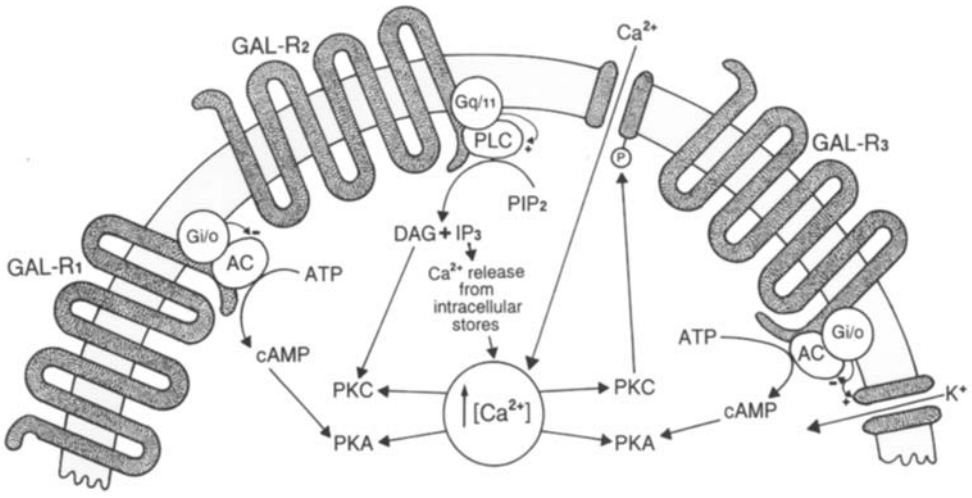

Figure 3. The main signaling pathways of galanin-receptor subtypes. DAG, diacylglycerol; P, phosphorylation site; PIP_2, phosphatidylinositol biphosphate. Other abbreviations are indicated in the text.

adrenal gland was shown to increase upon splanchnic-nerve stimulation (90). RIA indicated that the adrenal content of galanin varies from 3 to 90-115 pmol/g in humans, pigs and rats, which, according to Nussdorfer (91), could give rise to local concentrations ranging from 10^{-8} to 10^{-6} M. ICC confirmed the presence of galanin-IR in the chromaffin cells of the mammalian adrenal medulla and human pheochromocytomas (92-96), as well as in the avian interrenals (94). Galanin-positive nerve fibers have been traced both in the zona glomerulosa and adrenal medulla of rats, guinea pigs and hamsters (75,89,94), and in the frog interrenals (97).

The adrenal distribution of galanin receptors has been far less investigated. Recent findings showed the expression of GAL-R_1 and GAL-R_2, but not GAL-R_3, mRNAs in the zona fasciculata-reticularis (ZF/R) cells of the rat adrenals (98). Indirect evidence also indicated that GAL-R_1 and GAL-R_2 are expressed as proteins in both rat adrenal cortex and medulla (see 'Effects of galanin on the HPA axis. Adrenal medulla and adrenal cortex').

4. Effects of galanin on the HPA axis

Hypothalamus. Consisting findings indicate that galanin plays a role in the regulation of hypothalamic AVP biosynthesis and release and of water balance, at least in the rat (41,99-104). In fact, galanin intracerebroventricular (icv) administration was found to prevent the rise in both AVP expression in the hypothalamus and in AVP plasma level induced by hypertonic saline treatment or water restriction. The galanin antagonist galantide has been reported to raise hypothalamic AVP mRNA expression in dehydrated rats, suggesting a tonic inhibitory action of endogenous galanin (103). The action of galanin in euhydrated rats is negligible, although findings seem to suggest that icv galanin administration inhibits hypothalamic AVP biosynthesis, without affecting AVP blood levels (105). Due to the well-known aldosterone secretagogue action of AVP (reviewed in ref. 91), collectively these observations may account for the moderate galanin-induced decrease in plasma aldosterone in water-restricted rats (91,100,103) but not in euhydrated animals (106,107).

The effects of galanin on CRH biosynthesis and release have been far less investigated. Evidence has been provided that galanin (minimal effective concentration, $2x10^{-5}$ M) enhances by ~8-fold CRH (and neuropeptide-Y) secretion from perifused fetal rat hypothalamic neurons (108).

Pituitary gland. Galanin has been reported to inhibit *in vitro* ACTH secretion from rat pituitary corticotrophs (65,109,110), the effect being quenched by galanin immuno-neutralization (65). Accordingly, galanin intravenous (i.v.) administration was found to slightly lower basal ACTH plasma concentration in healthy human volunteers and to blunt ACTH response to CRH (111). However, in the rat the acute subcutaneous (s.c.) galanin injection was shown to evoke a significant rise in the blood level of ACTH (107,112), although the prolonged galanin administration (for up to 4 days) is ineffective (112). These findings, taken together with those reviewed in the above subsection, suggest that in the rat galanin acutely stimulates the central branch of the HPA axis, a contention in keeping with the demonstration that galanin *in vivo* administration increases the blood levels of corticosterone, the main glucocorticoid hormone in rodents (106,107,112-114).

Adrenal medulla. *In vivo* studies on the effects of galanin on adrenal medulla secretion gave rather controversial results, perhaps depending on the species examined and the route of galanin administration. Galanin i.v. infusion was shown to lower basal and insulin hypoglycemia-stimulated plasma norepinephrine (NE), but not epinephrine (E), levels in human volunteers (115). Galanin infusion has been reported to increase E, but not NE, plasma concentration in response to psychological stress in rats, without apparently affecting the basal level (116). Conversely, the injection of galanin into the rat PVN was found to raise within 24 h the basal plasma concentration of NE, but not E (117). Recent *in vitro* studies provided the first evidence that galanin (from 10^{-8} to 10^{-6} M)

enhances NE, but not E, secretion from rat adrenomedullary tissue (77).

Adrenal cortex. In addition to modulating adrenocortical secretion indirectly, i.e. acting on the central branch of the HPA axis, galanin also exerts a direct effect on the adrenal cortex, which, in the rat, appears to be mainly addressed to ZF/R. Galanin was found to increase corticosterone secretion from freshly dispersed rat inner adrenocortical cells, the effect being blocked by the aspecific galanin-receptor antagonist galantide (106,118,119). In this context, it appears of interest to mention evidence indicating that galanin, whose mRNA has been detected in the rat testis (74), is able to enhance either basal or agonist-stimulated testosterone secretion from dispersed rat Leydig cells, and that galantide prevents testosterone secretagogue action of galanin (120). Subsequent studies confirmed the *in vitro* corticosterone secretagogue action of galanin, and provided insight into the receptor subtypes involved and their signaling mechanism (98). Galanin was shown to increase, in addition to corticosterone secretion, also cAMP (but not IP_3) release from rat ZF/R cells, minimal and maximal effective concentrations being 10^{-10} and 10^{-8} M, respectively. All these effects were partially blocked by the immuno-neutralization of either GAL-R_1 or GAL-R_2, and completely abolished by the simultaneous blockade of both receptor subtypes. GAL-R_3 immuno-blockade was ineffective, a finding in keeping with the fact that rat inner adrenocortical cells are not provided with this receptor subtype (see 'Expression of galanin and its receptors in the HPA axis. Adrenal gland'). Both the PKA inhibitor H-89 and the AC inhibitor SQ-22536 were shown to abolish corticosterone response of dispersed ZF/R cells to 10^{-8} M galanin, while the PLC inhibitor U-73122 and the PKC inhibitor calphostin-C were ineffective. In light of these observations, the conclusion was drawn that galanin stimulates corticosterone secretion from rat adrenocortical cells through GAL-R_1 and GAL-R_2 coupled to the AC/PKA-dependent signaling pathway. It is to be pointed out that these findings are in contrast with the currently accepted signaling mechanisms of GAL-R_1 and GAL-R_2 (see 'Biology of galanin and its receptors'), which accords well with the view that the signaling mechanisms of receptors may vary depending on the tissue and cell type.

Evidence has been provided that several regulatory peptides (e.g. vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, neuropeptide-Y, tachykinins, endothelins, adrenomedullin, cerebellin and atrial natriuretic peptide) are able to modulate adrenocortical functions via a paracrine mechanism, involving the release from medullary chromaffin cells of catecholamines, which in turn stimulate secretion of adrenocortical cells via ß-adrenoceptors located on them (25,121-127). There is proof that galanin may be included in this group of regulatory peptides. It has been found that: i) galanin enhances NE release from rat adrenal medulla (see above); and ii) the ß-adrenoceptor antagonist *l*-alprenolol partially prevents galanin-stimulated corticosterone secretion from adrenal slices containig medullary chromaffin tissue (77,106).

The physiological relevance of the adrenocortical secretagogue action of galanin remains uncertain in light of the fact that, under normal circumstancies, the blood levels of the peptide do not exceed 10^{-10} M in rats (128), i.e. its minimal *in vitro* effective concentration (see above). However, the release from medullary chromaffin cells of galanin may give rise to local concentrations of $10^{-8}/10^{-6}$ M, i.e. higher that its maximal effective concentration (see 'Expression of galanin and its receptors in the HPA axis. Adrenal gland'), making it likely an autocrine/paracrine regulatory action of this peptide. A physiological regulatory role of endogenous galanin has been suggested by the observation that the prolonged administration of galantide causes a sizeable decrease in the basal plasma corticosterone concentration in rats (113). Recent studies gave support to this contention (77). In fact, the galanin immunoneutralization, obtained with antibody concentrations able to suppress galanin glucocorticoid secretagogue effect on dispersed rat ZF/R cells, was shown to lower basal corticosterone production from adrenal slices containing medullary tissue, without affecting that from dispersed adrenocortical cells. These findings strongly suggest that in the rat endogenous galanin secreted from medullary chromaffin cells may be involved in the maintenance of a normal basal glucocorticoid secretion from adrenal cortex.

An opposite role for endogenous galanin has been reported in rats with regenerating adrenal cortex after gland enucleation and contralateral adrenal removal (114,129). The aspecific galanin-receptor antagonist [D-Thr^6,D-Trp^{8,9},15-ol]-galanin (1-15) administration (three s.c. injections 28, 16 and 4 h before the sacrifice) was shown to markedly increase both the blood level of corticosterone and the mitotic index of regenerating gland. Galanin administration was *per se* ineffective, but blocked the effects of the antagonist. The conclusion was drawn that endogenous galanin exerts a tonic inhibitory action on rat adrenal regeneration. In this connection, it is worth mentioning that other peptides possessing a stimulating action on normal adrenal cortex, e.g. AVP, Met-enkephalin and cholecystokinin (reviewed in refs. 23,91), have been shown to exert a tonic inhibitory effect on the secretion and growth of regenerating adrenal cortex (130-132).

Before concluding, it is to be recalled that galanin has been reported to exert a direct inhibitory action on the amphibian interrenal gland (97). Galanin (from 10^{-9} to $3x10^{-6}$ M) was shown to induce a dose-dependent inhibition of corticosterone and aldosterone release from perifused frog interrenal slices. Moreover, repeated pulses of 10^{-6} M galanin at 90-min intervals were found to reduce the steroidogenic response to ACTH, but not angiotensin-II.

5. Involvement of galanin in the pathophysiology of the HPA axis

Modulation of responses to stresses. Findings are available that in the rat galanin, either systemically or centrally administered, enhances basal and stress-induced sympathetic outflow, as evidenced by the rise in the plasma levels of catecholamines (116,117). Malendowicz *et al* (107) examined the short-term effects of systemic galanin administration on the rat HPA-axis response to ether and cold stresses. They found that ether stress exerts a markedly stronger HPA-axis stimulation than cold stress. Galanin was shown to potentiate ACTH response to ether, but not cold stress, suggesting that the galaninergic mechanisms involved in the stimulation of ACTH secretion do

not interfere with ether stress-activated ones and are probably similar to those underlying the cold-stress action. Galanin did not affect the intense corticosterone response to ether stress, but within 60 min magnified the cold stress-induced moderate rise in corticosterone plasma concentration. These investigators concluded that steroidogenic capacity of adrenal cortex, as least in terms of glucocorticoid hormones, is a rate-limiting step in the response of rat HPA axis to severe stress, and that the direct secretagogue action of galanin on the adrenal cortex (see 'Effects of galanin on the HPA axis. Adrenal cortex') can manifest itself only in the case of the submaximally cold stress-stimulated HPA axis.

In this connection, it is of interest to mention that other regulatory peptides, including some of those which, like galanin, regulate feeding (see Introduction), have been reported to exert different effects on rat HPA-axis responses to ether and cold stresses. To summarize, evidence has been provided that i) substance-P potentiates ACTH response to ether stress and dampens that to cold stress (133); ii) proadrenomedullin N-terminal 20 peptide depresses HPA-axis response to cold stress, without affecting that to ether stress (134); iii) leptin impairs ACTH response to ether stress, but potentiates that to cold stress (135); iv) orexin-A magnifies ACTH response to cold, but not ether stress (136); and v) beacon suppresses ACTH response to ether, but not cold stress (12).

Pituitary adenomas. Findings showed that in many pituitary adenomas galanin-positive cells were almost exclusively corticotrophs (69), although some ACTH-secreting adenomas did not express galanin (70). Direct evidence is lacking, but some observations may suggest that galanin is involved in the development of pituitary-cell hyperplasia and tumorigenesis. Galanin mRNA expression was found to be markedly increased in estrogen-induced rat lactotroph hyperplasia (56,58,60,62,66,73,137-141) and prolactinomas (66,73,139,140,142,143). Human growth hormone-releasing hormone (GHRH) was shown to enhance galanin release from dispersed mouse anterior pituitary cells, and human GHRH-gene transgenic mice were found to develop somatotroph adenomas associated with elevated galanin-mRNA expression (142,144,145). The appealing possibility that endogenous galanin acts as an autocrine/paracrine growth and tumor promoter in the anterior pituitary remains to be addressed.

Pheochromocytomas. Studies carried out on a series of 16 pheochromocytomas revealed a galanin concentration ~8-fold higher than that in the normal adrenal tissue (21.0 versus 2.6 pmol/g) (80). Human pheochromocytomas are known to synthesize and secrete, in addition to catecholamines, a pleiad of peptides (e.g. CRH, proopiomelanocortin-derived peptides, endorphins, enkephalins, leptin, orexins, neuropeptide-Y, substance-P, vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, calcitonin gene-related peptide, adrenomedullin, proadenomedullin N-terminal 20 peptide, somatostatin and natriuretic peptides), that may variously modulate their functions (reviewed in refs. 13,16,25,91,121,126,146). Could galanin be included in this group of peptides regulating pheochromocytoma secretion?

6. Concluding remarks

The preceding sections of this survey have shown that, in the 18 years elapsed from the discovery of galanin, considerable amount of data has been accumulated indicating that this peptide plays a potentially important role in the autocrine/paracrine functional regulation on the central and peripheral branches of the HPA axis.

We consider the following topics of interest for future investigations: i) the effects of galanin on aldosterone and medullary catecholamine secretion are doubtful, and surely merit further study; ii) the majority of investigations have been carried out in rodents, and their results need to be confirmed in humans: for example, neither galanin-receptor expression nor *in vitro* galanin secretory effects have been examined in human adrenals and adrenal tumors; and iii) the response of HPA axis to stresses must be studied in galanin-gene knocked-out mice or in animals where the galanin system had been pharmacologically suppressed.

The elucidation of these and many other basic topics, along with the development of new selective and potent antagonists of galanin receptors, will not only increase our knowledge of the physiology of the HPA axis, but also, and more importantly, will shed light on possible novel strategies in the therapy of diseases caused by or causing dysregulation of adrenal functions.

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