Experientia Supplementum 102

Galanin

Bearbeitet von
Tomas Hökfelt

1. Auflage 2010. Buch. x, 286 S. Hardcover
ISBN 978 3 0346 0227 3
Format (B x L): 15,5 x 23,5 cm
Gewicht: 662 g

Galanin, Galanin Receptors, and Drug Targets

K. Mitsukawa, X. Lu, and T. Bartfai

Abstract Galanin, a neuropeptide widely expressed in the central and peripheral nervous systems and in the endocrine system, has been shown to regulate numerous physiological and pathological processes through interactions with three G-protein-coupled receptors, GalR1 through GalR3. Over the past decade, some of the receptor subtype-specific effects have been elucidated through pharmacological studies using subtype selective ligands, as well as through molecular approaches involving knockout animals. In this chapter, we summarize the current data which constitute the basis of targeting GalR1, GalR2, and GalR3 for the treatment of various human diseases and pathological conditions, including seizure, Alzheimer's disease, mood disorders, anxiety, alcohol intake in addiction, metabolic diseases, pain and solid tumors.

Keywords Drug treatment · Galanin receptor ligands · G-protein-coupled receptors · Neuropeptides · Therapeutics

Introduction

Galanin is a widely expressed neuropeptide that has three known receptors GalR1–3 (cf. Table 1), each of which are members of the G-protein-coupled receptor (GPCR) superfamily. By the use of pharmacological agents, by studies on the GalR1 and GalR2 knockouts, and by use of galanin overexpressing transgenic animals, the three galanin receptors have been implicated, through central

K. Mitsukawa, X. Lu, and T. Bartfai (✉)
Molecular and Integrative Neurosciences Department, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
e-mail: tbartfai@scripps.edu

T. Hökfelt (ed.), *Galanin*, Experientia Supplementum 102,
DOI 10.1007/978-3-0346-0228-0_2,

Table 1 Distribution of galanin and the galanin receptor subtypes

	CNS								Pancreas	Solid tumors
	BNST	Amygdala	Hippocampus	Hypothalamus	DRN	Locus coeruleus	Spinal cord	DRG		
Galanin	+++	+++	+	+++	+	+++	++	++	+	++
GalR1	+++	+++	++	+++	++	+++	++	+++	+++	+++
GalR2	++	++	++	++	++	++	++	+++	++	++
GalR3	+/0	+/0	+/0	+	+/0	+/0	+/0	+/0	NA	NA
References	[1–22]								[10, 23–30]	[6, 31–39]

BNST bed nucleus of the stria terminalis; *DRG* dorsal root ganglia; *DRN* dorsal raphe nucleus; *GalR* galanin receptor; *NA* not applicable

Table 2 Involvement of galanin receptor subtypes in different physiological and pathological functions

Various physiological and pathological effects	Involved receptor subtype(s)	References
Feeding	GalR1 in the hypothalamus	[40–43]
Learning and memory	GalR1 and GalR2 in the hippocampus	[44–49]
Seizure	GalR1 and GalR2 in the hippocampus	[40, 44, 49–54]
Pain	GalR1 and GalR2 in the spinal cord and the DRG	[5, 6, 51, 55–57]
Anxiety and mood disorders	GalR1, GalR2 and GalR3 in the DRN, the hypothalamus, the locus coeruleus, the amygdala and BNST	[58–67]
Tumor	GalR1 and GalR2	[6, 32, 68, 69]

mechanisms, in the control of feeding, alcohol intake, seizure threshold, cognitive performance and mood, and through peripheral mechanisms in the control of pain threshold. Neurogenesis promotion by galanin acting at GalR2 receptors has also been found. Galanin and galanin receptor expression is becoming an increasingly used marker for certain solid tumors (cf. Table 2). The receptor subtypes and the proof-of-concept experiments that led to the identification of the three galanin receptor subtypes as putative drug targets in different disease states are described in this chapter.

Galanin and Galanin Receptor Agonists

Galanin is one of the most inducible neuropeptides. Its biosynthesis is increased 2–10-fold upon axotomy in the periphery [70–74] and upon seizure activity in the brain (reviewed in [50, 75]). Increased galanin concentrations appear to be neuroprotective [76–80] and to promote neurogenesis [1, 44, 51, 79]. These observations suggest that agonists of galanin receptors (GalR1–3) may be useful therapeutic agents in neuroprotection. Using the transgenic mice strain null for GalR1 and for GalR2, it could be clearly delineated that neuroprotective effects are due to activation of both GalR1 and GalR2 receptors in the hippocampus during seizure activity. The neurogenesis-promoting effects of galanin appear to be exerted at the GalR2 receptor subtype alone [51].

The available galanin receptor agonists are either of peptide type, like the endogenous peptide galanin – a ligand that acts as a full agonist at all three galanin receptor subtypes – or nonpeptide type with relatively low affinity (micromolar) and without receptor subtype selectivity, like Galnon and Galmic, both of which acts at both GalR1 and GalR2 receptors (cf. Table 4). Thus it is hard to carry out conclusive pharmacological experiments regarding the receptor subtype selective agonists.

Nevertheless, by the combination of the results from transgenic animals null for specific galanin receptor subtypes and the use of the above-described agonists, it is

Table 3 Galanin receptor ligands as putative therapeutic targets

Galanin receptor ligands		Various indicated therapeutic aspects	References
GalR1	Agonist	Analgesic, anticonvulsant, anxiolytic	[5, 40, 50–52, 54–56, 61, 94, 96, 102]
	Antagonist	Antidepressant, cognitive enhancement, regulation of feeding	[40, 41, 51, 62, 103–107]
GalR2	Agonist	Analgesic, anticonvulsant, antidepressant, anxiolytic, neuroprotection/ neuroregeneration	[5, 44, 50, 54, 55, 57, 58, 60, 62, 71, 79, 80, 94, 96, 102]
GalR3	Antagonist	Antidepressant, anxiolytic, block alcohol intake in addiction	[59, 101, 108, 109]

now well established that both agonists and antagonists for the three galanin receptor subtypes can be used as putative therapeutics targets (cf. Table 3).

Galanin Receptor Subtypes in Regulation of Seizure Threshold, Seizure Initiation, and Maintenance

It was shown early on that galanin can inhibit glutamate but not GABA release in the hippocampus [110], suggesting that galanin will be useful in changing the excitatory tone in the hippocampus without suppressing the inhibitory tone. Such an agent was predicted to possess anticonvulsant properties.

Indeed, transgenic and pharmacological experiments on galanin receptor subtypes show that one of the most promising avenues towards novel anticonvulsant and antiepileptic agent includes development of galanin receptor agonists.

The hyperpolarizing actions exerted by galanin at hippocampal GalR1 receptor are playing an important role in setting the seizure threshold. Two transgenic experimental models indicated the robustness of galanin action as an antiepileptic and anticonvulsant agent:

1. The GalR1 null mutation mouse has spontaneous seizures [40, 52, 111], suggesting that a GalR1 subtype selective agonist may be a useful antiepileptic agent.
2. The galanin-overexpressing mouse that has 2–5-fold higher galanin levels in the forebrain because of the PDGF-beta promoter-directed overexpression of galanin required twice as many kindling events for spontaneous seizure development as the wild-type littermates with normal galanin expression in models of kindling epileptogenesis [112, 113]. These experiments showed that pharmacologically applied galanin agonists, above the endogenous levels of galanin, should be a potent useful antiepileptic. The experiments, however, have not determined whether it is GalR1, GalR2 or GalR3 agonists or mixed subtype nonselective agonists that are required for this action since galanin is a pan ligand for all three galanin receptor subtypes.

The pharmacological experiments using Galnon [94] and Galmic [51], both of which are mixed GalR1/GalR2 receptor agonists, have shown that the best

anticonvulsant effect is achieved by a mixed agonist. Several laboratories and companies are in the process of synthesizing analogs to these two compounds with the aim of developing these compounds as antiepileptics.

Galanin, Cognition and Neuroprotection in Alzheimer's Disease

Intracerebroventricularly (i.c.v) injected galanin [103] impairs the performance of mice in the Morris water maze. The subsequent dozens of studies on the effects of galanin on LTP (long-term potentiation) [45, 81, 114, 115] and on various cognitive tasks [46, 116] showed that in normal young animals intrahippocampal or i.c.v. galanin impairs learning and cognitive performance. A closer look at the cellular basis of this phenomenon has shown that galanin, which is coexpressed with acetylcholine in the nucleus basalis cholinergic neurons that project to the hippocampus, can inhibit acetylcholine release [117]. Galanin also coexists with noradrenaline [118–120] and serotonin [58, 120, 121] and is expressed in the noradrenergic and serotonergic projections to the hippocampus. The first conclusion one can draw from these data is that galanin receptor antagonists should be useful as cognitive enhancers because they would disinhibit the release of acetylcholine. This becomes truly important in Alzheimer's disease, which is characterized by the progressive degeneration of the cholinergic/galaninergic neurons. The loss of cholinergic neurons is accompanied by an increase in the firing rate of the surviving cholinergic neurons. Therefore, one can speculate that if galanin-mediated inhibition can be removed by galanin receptor antagonists, then the surviving cholinergic neurons should be expected to compensate better the pathology by replacing more acethylcholine. It has also been found from human autopsy studies that galanin-like immune reactivity and galanin receptor expression levels are elevated in Alzheimer's disease afflicted brains [122–124]. In particular, Mufson and his colleagues have shown that in Alzheimer's disease, the surviving cholinergic basal forebrain neurons were hyperinnervated by galaninergic fibers [104, 105]. One possibility would be, as suggested by these authors, that galanin hyperinnervation actually contributes to the pathogenesis by promoting the loss of cholinergic neurons, and this again is consistent with the utility of galanin receptor antagonists as potential treatments for Alzheimer's disease. The hippocampal galaninergic inhibition of acetylcholine release is believed to be exerted at GalR1 because the expression levels of another Gi-coupled galanin receptor, GalR3, are extremely low in the hippocampus and it is unclear how much GalR3-mediated actions contribute to the galanin effects in the hippocampus. Therefore, as a cognitive enhancer, GalR1 antagonists are expected to be useful in Alzheimer's disease, either alone or in conjunction with current therapies such as acetylcholinesterase (AChE) inhibitors.

GalR2 agonists were found to promote neuroprotection and neurogenesis [51, 71, 78–80]. Therefore, GalR2 agonists might help the treatment of cognitive disorders of neurodegenerative etiology.

Galanin, Mood Regulation and Alcohol Intake

GalR2 agonist: galanin is coexpressed with noradrenaline in almost 100% of the noradrenergic neurons in the locus coeruleus (LC) [118–120] and with serotonin in ca. 70% of the serotonergic neurons in the dorsal raphe nucleus (DRN) [58, 120, 121]. These two major monoaminergic nuclei play a key role in depression when the overactivity of the LC noradrenergic neurons leads to suppression of the firing of the DRN serotonergic neurons [125–128]. Uptake blockers of serotonin (SSRIs) and of both noradrenaline and serotonin (SNRIs) are effective therapeutic agents in the treatment of major depression. It was found by Lu et al. [58] that SSRI treatment elevated galanin mRNA and GalR2 receptor binding levels in the DRN (cf. Table 4). Subsequent experiments in depression-related animal models suggest that GalR2 agonists may be effective in the treatment of major depression. The GalR2 agonists, with expected anticonvulsant and antidepressant efficacy, fit well with a general observation that many anticonvulsants are also useful as mood stabilizers [129, 130].

The GalR3 receptor is the least abundantly expressed of the galanin receptor subtypes. Its distribution is deduced from in situ hybridization data, and it seems to be most densely expressed in the hypothalamus, where it is expressed still much weaker than GalR1 [2, 3].

It was a great surprise when Synaptic-Lundbeck disclosed that the company had synthesized two GalR3 subtype selective antagonists with nanomolar affinity, and that these compounds were active in some anxiety models like stress-induced hyperthermia and punished drinking and in some acute antidepressant models like forced swim and tail suspension tests [59].

Another GalR3 selective antagonist was synthesized by Rebek and tested in antidepressant models [101], where it confirmed the findings by Swanson et al. [59] that GalR3 antagonists have antidepressant-like activity. There is strong activity in the industry to synthesize additional GalR3 antagonists for clinical trials.

Both human genetic [108] and behavioral animal data [131, 132] have suggested that galanin action in the amygdala and elsewhere, is involved in addictive behavior such as repeated alcohol intake [133]. Indeed, GalR3 showed a significant association with alcoholism that was driven by one single nucleotide polymorphism, and there was no effect of GalR1 or GalR2 haplotypes on alcoholism risk [109]. This finding is of particular interest since mood disorders are often comorbid with alcoholism in humans. Therefore, development of galanin receptor antagonists, in particular GalR3 antagonists, might be a breakthrough in the addiction relevant field.

Galanin Receptor and Feeding Behavior

Galanin is a potent inhibitor of the glucose-induced insulin secretion from the pancreas [134].

The GalR1 receptor was first cloned from a human Bowes melanoma cell line and shortly after from a rat insulinoma cell line [4, 23]. Studies on pancreatic islets

Table 4 Galanin receptor ligands in preclinical and clinical experiments

Peptide type ligands				
Galanin	Nonselective agonist	i.v. (human), i.c.v., intrathecally, locally into the brain area	Analgesic, anticonvulsant, antidepressant-, anxiolytic-like, attenuated LTP in DG Impaired cognition Inhibited glucose-stimulated insulin release	[81–88]
Galanin (2–11)	GalR2/3 agonist	i.c.v., intrathecally, locally into the brain area	Anticonvulsant-like, analgesic, neuroprotection	[55, 89, 90]
M35, M40	Nonselective antagonist	i.c.v., intrathecally, locally into the brain area	Anxiolytic-like, blocked the antidepressant-induced effect, induced a significant allodynic state in nonallodynic rats, blocked galanin-induced effects in feeding, cognition, seizure and depression model	[58, 64, 86, 91–93]
Nonpeptide type ligands				
Galnon, Galmic	GalR1/2 agonist	i.p.	Anticonvulsant, antidepressant-, anxiolytic-like, attenuated LTP in DG, Stimulated insulin release	[44, 58, 81, 94–98]
[a]SNAP37889, [a]SNAP398299	GalR3 antagonist	p.o.	Antidepressant-, anxiolytic-like	[59, 99, 100]
3-(3,4-dichloro-phenylimino)-1-(6-methoxy-pyridin-3-yl) indolin-2-one	GalR3 antagonist	i.p.	Antidepressant-like	[101]

[a]Clinical trials in 2005–2006 (disclosers from Synaptic-Lundbeck), *i.v.* intravenously; *i.p.* intraperitoneally; *p.o.* per os

show that it is the GalR1 subtype that hyperpolarizes the islets through Gi protein-K channel coupling, which leads to inhibition of insulin secretion.

Galanin, when injected into the lateral ventricle or directly into the paraventricular nucleus of the hypothalamus [135–139], strongly induces feeding. The choice of food, if protein carbohydrates and fat are available, is directed towards fat preference [140].

Galanin is rapidly induced in the rat PVN (periventricular nucleus) upon fat intake [139]. Detailed metabolic chamber and meal composition studies on GalR1 null mutation carrying mice show that this receptor subtype mediates important effects that are required for glycemic control and body weight control [41].

The above data point to the therapeutic usefulness of GalR1 ligands in metabolic diseases.

Galanin in Pain Syndromes

Galanin is expressed in both sensory and spinal cord interneurons and thus plays a key gatekeeper role in pain signaling [141]. Nerve injury such as axotomy leads to a rapid induction of galanin expression in the sensory ganglia [73, 74, 142, 143]. Galanin has a biphasic response in many pain models, with low galanin doses (intrathecally) escalating and high doses suppressing pain [5, 55].

It has been speculated that GalR1-mediated hyperpolarization of the sensory and interneurons is responsible for the analgesic effect and for the synergistic effect with opiates. GalR1 agonists are suggested to suppress glutamate release in the spinal cord [144]. The GalR2-mediated depolarizing effects, while important for neuroregeneration, may contribute to pain sensation.

There is a strong effort in progress to find GalR1 agonists for systemic or intrathecal use in pain therapy.

Galanin and Tumors

Galanin and galanin receptors have been found in several endocrine tumors, for example pancreatic, hypothalamic and pituitary tumors [6, 31, 32, 145–149]. Clinical data were published on pancreatic tumor therapy, which now includes galanin in addition to the somatostatin receptor agonists' octeroide and serotonin.

Small cell lung carcinoma and colon cancer isolates have also been shown to express galanin and GalR1 [23, 33] and in some cases GalR2 [34]. GalR2 signaling in small cell lung carcinomas has been studied in detail, and the influence of GalR2 on tumor growth has been shown [34, 150].

Galanin Receptor Ligands in Development

Galanin receptors (GalR1–3) are members of the GPCR superfamily. These seven transmembrane receptor proteins are among the favorite drug targets of the pharmaceutical industry. Widely prescribed drugs such as alpha and beta adrenergic blockers (used in hypertension and heart diseases), dopamine D2 receptor antagonists (used in psychosis), dopamine receptor agonists (used in Parkinson's disease), histamine H1 receptor antagonists (used in allergy common cold and motion sickness) and histamine H2 receptor antagonists (used in peptic ulcer diseases) are all ligands for GPCRs.

In view of the strong biological data as outlined above in several therapeutic areas, the pharmaceutical industry and academia have been searching for nonpeptide type galanin receptor ligands that would have better stability than galanin, the peptide that is metabolized in minutes in humans, and which would cross the blood–brain barrier to be able to act at the central galanin receptors.

Despite the relatively easy way to find hits for many GPCRs, after screening ca. six million compounds at big pharmaceutical industry, no high-affinity (submicromolar affinity) and chemically workable (easy-to-develop analogs that have higher affinity with better pharmacological profile) compounds have yet been found.

The presently available nonpeptide galanin receptor ligands are the GalR3 antagonists discovered by Synaptic-Lundbeck, which according the publication by Swanson et al. [59], have high affinity (nanomolar) and high selectivity (50–100-fold over GalR1 and -2) [59]. These compounds exhibit antidepressant and anxiolytic efficacies in animal models.

The nonpeptide galanin receptor agonists Galnon [94, 95] and Galmic [44] are micromolar to submicromolar affinity and are not selective between GalR1 and GalR2 receptors. In the therapeutic indication of epilepsy, a nonselective GalR1/GalR2 agonist is advantageous, as GalR1 and GalR2 signaling suppress the initiation and maintenance of seizures, respectively [50]. However, for the indications of depression, pain and neuroprotection, subtype selective galanin agonists would be desirable. In addition, the therapeutic indications of cognitive enhancement and feeding regulation call for subtype-selective GalR1 antagonists.

We are confident that subtype selective high-affinity agonists and antagonists for the galanin receptor subtypes will be found because the biological data are compelling for their therapeutic benefits.

Acknowledgments This study was supported by National Institutes of Mental Health (NIMH) grant RO1MH63080–05 and MH074055–01 to T. Bartfai and the Japan Society for the Promotion of Science (JSPS) Postdoctoral Fellowship for Research Abroad, Swiss National Science Foundation and Novartis Foundation, formerly the Ciba-Geigy Jubilee Foundation to K. Mitsukawa.

References

1. Shen PJ, Larm JA, Gundlach AL (2003) Expression and plasticity of galanin systems in cortical neurons, oligodendrocyte progenitors and proliferative zones in normal brain and after spreading depression. Eur J Neurosci 18:1362–1376
2. Waters SM, Krause JE (2000) Distribution of galanin-1, -2 and -3 receptor messenger RNAs in central and peripheral rat tissues. Neuroscience 95:265–271
3. Mennicken F, Hoffert C, Pelletier M, Ahmad S, O'Donnell D (2002) Restricted distribution of galanin receptor 3 (GalR3) mRNA in the adult rat central nervous system. J Chem Neuroanat 24:257–268
4. Parker EM, Izzarelli DG, Nowak HP, Mahle CD, Iben LG, Wang J, Goldstein ME (1995) Cloning and characterization of the rat GALR1 galanin receptor from Rin14B insulinoma cells. Brain Res Mol Brain Res 34:179–189

5. Liu HX, Hokfelt T (2002) The participation of galanin in pain processing at the spinal level. Trends Pharmacol Sci 23:468–474
6. Lang R, Gundlach AL, Kofler B (2007) The galanin peptide family: receptor pharmacology, pleiotropic biological actions, and implications in health and disease. Pharmacol Ther 115:177–207
7. Ryan MC, Gundlach AL (1996) Localization of preprogalanin messenger RNA in rat brain: identification of transcripts in a subpopulation of cerebellar Purkinje cells. Neuroscience 70:709–728
8. Jacobowitz DM, Kresse A, Skofitsch G (2004) Galanin in the brain: chemoarchitectonics and brain cartography–a historical review. Peptides 25:433–464
9. Cheung CC, Hohmann JG, Clifton DK, Steiner RA (2001) Distribution of galanin messenger RNA-expressing cells in murine brain and their regulation by leptin in regions of the hypothalamus. Neuroscience 103:423–432
10. Kolakowski LF Jr, O'Neill GP, Howard AD, Broussard SR, Sullivan KA, Feighner SD, Sawzdargo M, Nguyen T, Kargman S, Shiao LL et al (1998) Molecular characterization and expression of cloned human galanin receptors GALR2 and GALR3. J Neurochem 71:2239–2251
11. Smith KE, Walker MW, Artymyshyn R, Bard J, Borowsky B, Tamm JA, Yao WJ, Vaysse PJ, Branchek TA, Gerald C et al (1998) Cloned human and rat galanin GALR3 receptors. Pharmacology and activation of G-protein inwardly rectifying K+ channels. J Biol Chem 273:23321–23326
12. O'Donnell D, Ahmad S, Wahlestedt C, Walker P (1999) Expression of the novel galanin receptor subtype GALR2 in the adult rat CNS: distinct distribution from GALR1. J Comp Neurol 409:469–481
13. Landry M, Bouali-Benazzouz R, Andre C, Shi TJ, Leger C, Nagy F, Hokfelt T (2006) Galanin receptor 1 is expressed in a subpopulation of glutamatergic interneurons in the dorsal horn of the rat spinal cord. J Comp Neurol 499:391–403
14. Brumovsky P, Mennicken F, O'Donnell D, Hokfelt T (2006) Differential distribution and regulation of galanin receptors- 1 and -2 in the rat lumbar spinal cord. Brain Res 1085:111–120
15. Zhang X, Nicholas AP, Hokfelt T (1993) Ultrastructural studies on peptides in the dorsal horn of the spinal cord – I.Co-existence of galanin with other peptides in primary afferents in normal rats. Neuroscience 57:365–384
16. Xu ZQ, Shi TJ, Landry M, Hokfelt T (1996) Evidence for galanin receptors in primary sensory neurones and effect of axotomy and inflammation. NeuroReport 8:237–242
17. Burgevin MC, Loquet I, Quarteronet D, Habert-Ortoli E (1995) Cloning, pharmacological characterization, and anatomical distribution of a rat cDNA encoding for a galanin receptor. J Mol Neurosci 6:33–41
18. Skofitsch G, Jacobowitz DM (1985) Immunohistochemical mapping of galanin-like neurons in the rat central nervous system. Peptides 6:509–546
19. Ch'ng JL, Christofides ND, Anand P, Gibson SJ, Allen YS, Su HC, Tatemoto K, Morrison JF, Polak JM, Bloom SR (1985) Distribution of galanin immunoreactivity in the central nervous system and the responses of galanin-containing neuronal pathways to injury. Neuroscience 16:343–354
20. Skofitsch G, Jacobowitz DM (1985) Galanin-like immunoreactivity in capsaicin sensitive sensory neurons and ganglia. Brain Res Bull 15:191–195
21. Hawes JJ, Picciotto MR (2004) Characterization of GalR1, GalR2, and GalR3 immunoreactivity in catecholaminergic nuclei of the mouse brain. J Comp Neurol 479:410–423
22. Larm JA, Shen PJ, Gundlach AL (2003) Differential galanin receptor-1 and galanin expression by 5-HT neurons in dorsal raphe nucleus of rat and mouse: evidence for species-dependent modulation of serotonin transmission. Eur J Neurosci 17:481–493
23. Habert-Ortoli E, Amiranoff B, Loquet I, Laburthe M, Mayaux JF (1994) Molecular cloning of a functional human galanin receptor. Proc Natl Acad Sci USA 91:9780–9783

24. Dunning BE, Ahren B, Veith RC, Bottcher G, Sundler F, Taborsky GJ Jr (1986) Galanin: a novel pancreatic neuropeptide. Am J Physiol 251:E127–E133
25. Lindskog S, Ahren B, Dunning BE, Sundler F (1991) Galanin-immunoreactive nerves in the mouse and rat pancreas. Cell Tissue Res 264:363–368
26. Ahren B, Ar'Rajab A, Bottcher G, Sundler F, Dunning BE (1991) Presence of galanin in human pancreatic nerves and inhibition of insulin secretion from isolated human islets. Cell Tissue Res 264:263–267
27. Shimosegawa T, Moriizumi S, Koizumi M, Kashimura J, Yanaihara N, Toyota T (1992) Immunohistochemical demonstration of galaninlike immunoreactive nerves in the human pancreas. Gastroenterology 102:263–271
28. Messell T, Harling H, Bottcher G, Johnsen AH, Holst JJ (1990) Galanin in the porcine pancreas. Regul Pept 28:161–176
29. Furuzawa Y, Ohmori Y, Watanabe T (1996) Immunohistochemical studies of neural elements in pancreatic islets of the cat. J Vet Med Sci 58:641–646
30. Baltazar ET, Kitamura N, Sasaki M, Cottrell DF, Boloron HM, Yamada J (2001) Galanin-like immunoreactive neural elements in domestic ruminant pancreas. J Vet Med Sci 63:841–848
31. Sano T, Vrontakis ME, Kovacs K, Asa SL, Friesen HG (1991) Galanin immunoreactivity in neuroendocrine tumors. Arch Pathol Lab Med 115:926–929
32. Berger A, Santic R, Hauser-Kronberger C, Schilling FH, Kogner P, Ratschek M, Gamper A, Jones N, Sperl W, Kofler B (2005) Galanin and galanin receptors in human cancers. Neuropeptides 39:353–359
33. Kim KY, Kee MK, Chong SA, Nam MJ (2007) Galanin is up-regulated in colon adenocarcinoma. Cancer Epidemiol Biomark Prev 16:2373–2378
34. Wittau N, Grosse R, Kalkbrenner F, Gohla A, Schultz G, Gudermann T (2000) The galanin receptor type 2 initiates multiple signaling pathways in small cell lung cancer cells by coupling to G(q), G(i) and G(12) proteins. Oncogene 19:4199–4209
35. Felix I, Bilbao JM, Asa SL, Tyndel F, Kovacs K, Becker LE (1994) Cerebral and cerebellar gangliocytomas: a morphological study of nine cases. Acta Neuropathol 88:246–251
36. Bauer FE, Hacker GW, Terenghi G, Adrian TE, Polak JM, Bloom SR (1986) Localization and molecular forms of galanin in human adrenals: elevated levels in pheochromocytomas. J Clin Endocrinol Metab 63:1372–1378
37. Sullivan KA, Shiao LL, Cascieri MA (1997) Pharmacological characterization and tissue distribution of the human and rat GALR1 receptors. Biochem Biophys Res Commun 233:823–828
38. Henson BS, Neubig RR, Jang I, Ogawa T, Zhang Z, Carey TE, D'Silva NJ (2005) Galanin receptor 1 has anti-proliferative effects in oral squamous cell carcinoma. J Biol Chem 280:22564–22571
39. Berger A, Santic R, Almer D, Hauser-Kronberger C, Huemer M, Humpel C, Stockhammer G, Sperl W, Kofler B (2003) Galanin and galanin receptors in human gliomas. Acta Neuropathol 105:555–560
40. Jacoby AS, Hort YJ, Constantinescu G, Shine J, Iismaa TP (2002) Critical role for GALR1 galanin receptor in galanin regulation of neuroendocrine function and seizure activity. Brain Res Mol Brain Res 107:195–200
41. Zorrilla EP, Brennan M, Sabino V, Lu X, Bartfai T (2007) Galanin type 1 receptor knockout mice show altered responses to high-fat diet and glucose challenge. Physiol Behav 91:479–485
42. Wynick D, Bacon A (2002) Targeted disruption of galanin: new insights from knock-out studies. Neuropeptides 36:132–144
43. Ahren B, Pacini G, Wynick D, Wierup N, Sundler F (2004) Loss-of-function mutation of the galanin gene is associated with perturbed islet function in mice. Endocrinology 145:3190–3196

44. Mazarati A, Lu X, Kilk K, Langel U, Wasterlain C, Bartfai T (2004) Galanin type 2 receptors regulate neuronal survival, susceptibility to seizures and seizure-induced neurogenesis in the dentate gyrus. Eur J Neurosci 19:3235–3244
45. Badie-Mahdavi H, Lu X, Behrens MM, Bartfai T (2005) Role of galanin receptor 1 and galanin receptor 2 activation in synaptic plasticity associated with 3', 5'-cyclic AMP response element-binding protein phosphorylation in the dentate gyrus: studies with a galanin receptor 2 agonist and galanin receptor 1 knockout mice. Neuroscience 133:591–604
46. Rustay NR, Wrenn CC, Kinney JW, Holmes A, Bailey KR, Sullivan TL, Harris AP, Long KC, Saavedra MC, Starosta G et al (2005) Galanin impairs performance on learning and memory tasks: findings from galanin transgenic and GAL-R1 knockout mice. Neuropeptides 39:239–243
47. Gottsch ML, Zeng H, Hohmann JG, Weinshenker D, Clifton DK, Steiner RA (2005) Phenotypic analysis of mice deficient in the type 2 galanin receptor (GALR2). Mol Cell Biol 25:4804–4811
48. Wrenn CC, Kinney JW, Marriott LK, Holmes A, Harris AP, Saavedra MC, Starosta G, Innerfield CE, Jacoby AS, Shine J et al (2004) Learning and memory performance in mice lacking the GAL-R1 subtype of galanin receptor. Eur J Neurosci 19:1384–1396
49. Blackshear A, Yamamoto M, Anderson BJ, Holmes PV, Lundstrom L, Langel U, Robinson JK (2007) Intracerebroventricular administration of galanin or galanin receptor subtype 1 agonist M617 induces c-Fos activation in central amygdala and dorsomedial hypothalamus. Peptides 28:1120–1124
50. Mazarati AM (2004) Galanin and galanin receptors in epilepsy. Neuropeptides 38:331–343
51. Bartfai T, Lu X, Badie-Mahdavi H, Barr AM, Mazarati A, Hua XY, Yaksh T, Haberhauer G, Ceide SC, Trembleau L et al (2004) Galmic, a nonpeptide galanin receptor agonist, affects behaviors in seizure, pain, and forced-swim tests. Proc Natl Acad Sci USA 101:10470–10475
52. Mazarati A, Lu X, Shinmei S, Badie-Mahdavi H, Bartfai T (2004) Patterns of seizures, hippocampal injury and neurogenesis in three models of status epilepticus in galanin receptor type 1 (GalR1) knockout mice. Neuroscience 128:431–441
53. Sadegh M, Mirnajafi-Zadeh J, Javan M, Fathollahi Y, Mohammad-Zadeh M, Jahanshahi A, Noorbakhsh SM (2007) The role of galanin receptors in anticonvulsant effects of low-frequency stimulation in perforant path-kindled rats. Neuroscience 150:396–403
54. Mazarati A, Lundstrom L, Sollenberg U, Shin D, Langel U, Sankar R (2006) Regulation of kindling epileptogenesis by hippocampal galanin type 1 and type 2 receptors: the effects of subtype-selective agonists and the role of G-protein-mediated signaling. J Pharmacol Exp Ther 318:700–708
55. Liu HX, Brumovsky P, Schmidt R, Brown W, Payza K, Hodzic L, Pou C, Godbout C, Hokfelt T (2001) Receptor subtype-specific pronociceptive and analgesic actions of galanin in the spinal cord: selective actions via GalR1 and GalR2 receptors. Proc Natl Acad Sci USA 98:9960–9964
56. Blakeman KH, Hao JX, Xu XJ, Jacoby AS, Shine J, Crawley JN, Iismaa T, Wiesenfeld-Hallin Z (2003) Hyperalgesia and increased neuropathic pain-like response in mice lacking galanin receptor 1 receptors. Neuroscience 117:221–227
57. Hobson SA, Holmes FE, Kerr NC, Pope RJ, Wynick D (2006) Mice deficient for galanin receptor 2 have decreased neurite outgrowth from adult sensory neurons and impaired pain-like behaviour. J Neurochem 99:1000–1010
58. Lu X, Barr AM, Kinney JW, Sanna P, Conti B, Behrens MM, Bartfai T (2005) A role for galanin in antidepressant actions with a focus on the dorsal raphe nucleus. Proc Natl Acad Sci USA 102:874–879
59. Swanson CJ, Blackburn TP, Zhang X, Zheng K, Xu ZQ, Hokfelt T, Wolinsky TD, Konkel MJ, Chen H, Zhong H et al (2005) Anxiolytic- and antidepressant-like profiles of the galanin-3 receptor (Gal3) antagonists SNAP 37889 and SNAP 398299. Proc Natl Acad Sci USA 102:17489–17494

60. Bailey KR, Pavlova MN, Rohde AD, Hohmann JG, Crawley JN (2007) Galanin receptor subtype 2 (GalR2) null mutant mice display an anxiogenic-like phenotype specific to the elevated plus-maze. Pharmacol Biochem Behav 86:8–20
61. Holmes A, Kinney JW, Wrenn CC, Li Q, Yang RJ, Ma L, Vishwanath J, Saavedra MC, Innerfield CE, Jacoby AS et al (2003) Galanin GAL-R1 receptor null mutant mice display increased anxiety-like behavior specific to the elevated plus-maze. Neuropsychopharmacology 28:1031–1044
62. Kuteeva E, Wardi T, Lundstrom L, Sollenberg U, Langel U, Hokfelt T, Ogren SO (2008) Differential role of galanin receptors in the regulation of depression-like behavior and monoamine/stress-related genes at the cell body level. Neuropsychopharmacology 33 (11):2573–2585
63. Echevarria DJ, Hernandez A, Diogenes A, Morilak DA (2005) Administration of the galanin antagonist M40 into lateral septum attenuates shock probe defensive burying behavior in rats. Neuropeptides 39:445–451
64. Khoshbouei H, Cecchi M, Morilak DA (2002) Modulatory effects of galanin in the lateral bed nucleus of the stria terminalis on behavioral and neuroendocrine responses to acute stress. Neuropsychopharmacology 27:25–34
65. Moller C, Sommer W, Thorsell A, Heilig M (1999) Anxiogenic-like action of galanin after intra-amygdala administration in the rat. Neuropsychopharmacology 21:507–512
66. Lu X, Sharkey L, Bartfai T (2007) The brain galanin receptors: targets for novel antidepressant drugs. CNS Neurol Disord Drug Targets 6:183–192
67. Karlsson RM, Holmes A (2006) Galanin as a modulator of anxiety and depression and a therapeutic target for affective disease. Amino Acids 31:231–239
68. Berger A, Lang R, Moritz K, Santic R, Hermann A, Sperl W, Kofler B (2004) Galanin receptor subtype GalR2 mediates apoptosis in SH-SY5Y neuroblastoma cells. Endocrinology 145:500–507
69. Kanazawa T, Iwashita T, Kommareddi P, Nair T, Misawa K, Misawa Y, Ueda Y, Tono T, Carey TE (2007) Galanin and galanin receptor type 1 suppress proliferation in squamous carcinoma cells: activation of the extracellular signal regulated kinase pathway and induction of cyclin-dependent kinase inhibitors. Oncogene 26:5762–5771
70. Landry M, Holmberg K, Zhang X, Hokfelt T (2000) Effect of axotomy on expression of NPY, galanin, and NPY Y1 and Y2 receptors in dorsal root ganglia and the superior cervical ganglion studied with double-labeling in situ hybridization and immunohistochemistry. Exp Neurol 162:361–384
71. Burazin TC, Gundlach AL (1998) Inducible galanin and GalR2 receptor system in motor neuron injury and regeneration. J Neurochem 71:879–882
72. Rutherfurd SD, Widdop RE, Louis WJ, Gundlach AL (1992) Preprogalanin mRNA is increased in vagal motor neurons following axotomy. Brain Res Mol Brain Res 14:261–266
73. Hokfelt T, Wiesenfeld-Hallin Z, Villar M, Melander T (1987) Increase of galanin-like immunoreactivity in rat dorsal root ganglion cells after peripheral axotomy. Neurosci Lett 83:217–220
74. Villar MJ, Cortes R, Theodorsson E, Wiesenfeld-Hallin Z, Schalling M, Fahrenkrug J, Emson PC, Hokfelt T (1989) Neuropeptide expression in rat dorsal root ganglion cells and spinal cord after peripheral nerve injury with special reference to galanin. Neuroscience 33:587–604
75. Lundstrom L, Elmquist A, Bartfai T, Langel U (2005) Galanin and its receptors in neurological disorders. Neuromol Med 7:157–580
76. Holmes FE, Mahoney S, King VR, Bacon A, Kerr NC, Pachnis V, Curtis R, Priestley JV, Wynick D (2000) Targeted disruption of the galanin gene reduces the number of sensory neurons and their regenerative capacity. Proc Natl Acad Sci USA 97:11563–11568
77. O'Meara G, Coumis U, Ma SY, Kehr J, Mahoney S, Bacon A, Allen SJ, Holmes F, Kahl U, Wang FH et al (2000) Galanin regulates the postnatal survival of a subset of basal forebrain cholinergic neurons. Proc Natl Acad Sci USA 97:11569–11574

78. Mahoney SA, Hosking R, Farrant S, Holmes FE, Jacoby AS, Shine J, Iismaa TP, Scott MK, Schmidt R, Wynick D (2003) The second galanin receptor GalR2 plays a key role in neurite outgrowth from adult sensory neurons. J Neurosci 23:416–421
79. Elliott-Hunt CR, Marsh B, Bacon A, Pope R, Vanderplank P, Wynick D (2004) Galanin acts as a neuroprotective factor to the hippocampus. Proc Natl Acad Sci USA 101:5105–5110
80. Elliott-Hunt CR, Pope RJ, Vanderplank P, Wynick D (2007) Activation of the galanin receptor 2 (GalR2) protects the hippocampus from neuronal damage. J Neurochem 100:780–789
81. Badie-Mahdavi H, Behrens MM, Rebek J, Bartfai T (2005) Effect of galnon on induction of long-term potentiation in dentate gyrus of C57BL/6 mice. Neuropeptides 39:249–251
82. McDonald MP, Gleason TC, Robinson JK, Crawley JN (1998) Galanin inhibits performance on rodent memory tasks. Ann N Y Acad Sci 863:305–322
83. Murck H, Held K, Ziegenbein M, Kunzel H, Holsboer F, Steiger A (2004) Intravenous administration of the neuropeptide galanin has fast antidepressant efficacy and affects the sleep EEG. Psychoneuroendocrinology 29:1205–1211
84. Bing O, Moller C, Engel JA, Soderpalm B, Heilig M (1993) Anxiolytic-like action of centrally administered galanin. Neurosci Lett 164:17–20
85. Post C, Alari L, Hokfelt T (1988) Intrathecal galanin increases the latency in the tail-flick and hot-plate test in mouse. Acta Physiol Scand 132:583–584
86. Liu H, Hokfelt T (2000) Effect of intrathecal galanin and its putative antagonist M35 on pain behavior in a neuropathic pain model. Brain Res 886:67–72
87. Mazarati AM, Halaszi E, Telegdy G (1992) Anticonvulsive effects of galanin administered into the central nervous system upon the picrotoxin-kindled seizure syndrome in rats. Brain Res 589:164–166
88. Lindskog S, Dunning BE, Martensson H, Ar'Rajab A, Taborsky GJ Jr, Ahren B (1990) Galanin of the homologous species inhibits insulin secretion in the rat and in the pig. Acta Physiol Scand 139:591–596
89. Pirondi S, Fernandez M, Schmidt R, Hokfelt T, Giardino L, Calza L (2005) The galanin-R2 agonist AR-M1896 reduces glutamate toxicity in primary neural hippocampal cells. J Neurochem 95:821–833
90. Mazarati AM, Baldwin RA, Shinmei S, Sankar R (2005) In vivo interaction between serotonin and galanin receptors types 1 and 2 in the dorsal raphe: implication for limbic seizures. J Neurochem 95:1495–1503
91. Mazarati AM, Liu H, Soomets U, Sankar R, Shin D, Katsumori H, Langel U, Wasterlain CG (1998) Galanin modulation of seizures and seizure modulation of hippocampal galanin in animal models of status epilepticus. J Neurosci 18:10070–10077
92. Corwin RL, Robinson JK, Crawley JN (1993) Galanin antagonists block galanin-induced feeding in the hypothalamus and amygdala of the rat. Eur J Neurosci 5:1528–1533
93. Crawley JN, Robinson JK, Langel U, Bartfai T (1993) Galanin receptor antagonists M40 and C7 block galanin-induced feeding. Brain Res 600:268–272
94. Saar K, Mazarati AM, Mahlapuu R, Hallnemo G, Soomets U, Kilk K, Hellberg S, Pooga M, Tolf BR, Shi TS et al (2002) Anticonvulsant activity of a nonpeptide galanin receptor agonist. Proc Natl Acad Sci USA 99:7136–7141
95. Sollenberg U, Bartfai T, Langel U (2005) Galnon – a low-molecular weight ligand of the galanin receptors. Neuropeptides 39:161–163
96. Wu WP, Hao JX, Lundstrom L, Wiesenfeld-Hallin Z, Langel U, Bartfai T, Xu XJ (2003) Systemic galnon, a low-molecular weight galanin receptor agonist, reduces heat hyperalgesia in rats with nerve injury. Eur J Pharmacol 482:133–137
97. Rajarao SJ, Platt B, Sukoff SJ, Lin Q, Bender CN, Nieuwenhuijsen BW, Ring RH, Schechter LE, Rosenzweig-Lipson S, Beyer CE (2007) Anxiolytic-like activity of the non-selective galanin receptor agonist, galnon. Neuropeptides 41:307–320
98. Quynh NT, Islam SM, Floren A, Bartfai T, Langel U, Ostenson CG (2005) Effects of galnon, a non-peptide galanin-receptor agonist, on insulin release from rat pancreatic islets. Biochem Biophys Res Commun 328:213–220

99. Konkel MJ, Packiarajan M, Chen H, Topiwala UP, Jimenez H, Talisman IJ, Coate H, Walker MW (2006) Amino substituted analogs of 1-phenyl-3-phenylimino-2-indolones with potent galanin Gal3 receptor binding affinity and improved solubility. Bioorg Med Chem Lett 16:3950–3954
100. Konkel MJ, Lagu B, Boteju LW, Jimenez H, Noble S, Walker MW, Chandrasena G, Blackburn TP, Nikam SS, Wright JL et al (2006) 3-arylimino-2-indolones are potent and selective galanin GAL3 receptor antagonists. J Med Chem 49:3757–3758
101. Barr AM, Kinney JW, Hill MN, Lu X, Biros S, Rebek J Jr, Bartfai T (2006) A novel, systemically active, selective galanin receptor type-3 ligand exhibits antidepressant-like activity in preclinical tests. Neurosci Lett 405:111–115
102. Walton KM, Chin JE, Duplantier AJ, Mather RJ (2006) Galanin function in the central nervous system. Curr Opin Drug Discov Dev 9:560–570
103. Sundstrom E, Archer T, Melander T, Hokfelt T (1988) Galanin impairs acquisition but not retrieval of spatial memory in rats studied in the Morris swim maze. Neurosci Lett 88:331–335
104. Mufson EJ, Kahl U, Bowser R, Mash DC, Kordower JH, Deecher DC (1998) Galanin expression within the basal forebrain in Alzheimer's disease. Comments on therapeutic potential. Ann N Y Acad Sci 863:291–304
105. Mufson EJ, Cochran E, Benzing W, Kordower JH (1993) Galaninergic innervation of the cholinergic vertical limb of the diagonal band (Ch2) and bed nucleus of the stria terminalis in aging, Alzheimer's disease and Down's syndrome. Dementia 4:237–250
106. Hartonian I, Mufson EJ, De Lacalle S (2002) Long-term plastic changes in galanin innervation in the rat basal forebrain. Neuroscience 115:787–795
107. Steiner RA, Hohmann JG, Holmes A, Wrenn CC, Cadd G, Jureus A, Clifton DK, Luo M, Gutshall M, Ma SY et al (2001) Galanin transgenic mice display cognitive and neurochemical deficits characteristic of Alzheimer's disease. Proc Natl Acad Sci USA 98:4184–4189
108. Belfer I, Hipp H, McKnight C, Evans C, Buzas B, Bollettino A, Albaugh B, Virkkunen M, Yuan Q, Max MB et al (2006) Association of galanin haplotypes with alcoholism and anxiety in two ethnically distinct populations. Mol Psychiatry 11:301–311
109. Belfer I, Hipp H, Bollettino A, McKnight C, Evans C, Virkkunen M, Albaugh B, Max MB, Goldman D, Enoch MA (2007) Alcoholism is associated with GALR3 but not two other galanin receptor genes. Genes Brain Behav 6:473–481
110. Zini S, Roisin MP, Langel U, Bartfai T, Ben-Ari Y (1993) Galanin reduces release of endogenous excitatory amino acids in the rat hippocampus. Eur J Pharmacol 245:1–7
111. Fetissov SO, Jacoby AS, Brumovsky PR, Shine J, Iismaa TP, Hokfelt T (2003) Altered hippocampal expression of neuropeptides in seizure-prone GALR1 knockout mice. Epilepsia 44:1022–1033
112. Kokaia M, Holmberg K, Nanobashvili A, Xu ZQ, Kokaia Z, Lendahl U, Hilke S, Theodorsson E, Kahl U, Bartfai T et al (2001) Suppressed kindling epileptogenesis in mice with ectopic overexpression of galanin. Proc Natl Acad Sci USA 98:14006–14011
113. Schlifke I, Kuteeva E, Hokfelt T, Kokaia M (2006) Galanin expressed in the excitatory fibers attenuates synaptic strength and generalized seizures in the piriform cortex of mice. Exp Neurol 200:398–406
114. Mazarati AM, Hohmann JG, Bacon A, Liu H, Sankar R, Steiner RA, Wynick D, Wasterlain CG (2000) Modulation of hippocampal excitability and seizures by galanin. J Neurosci 20:6276–6281
115. Sakurai E, Maeda T, Kaneko S, Akaike A, Satoh M (1996) Galanin inhibits long-term potentiation at Schaffer collateral-CA1 synapses in guinea-pig hippocampal slices. Neurosci Lett 212:21–24
116. Robinson JK (2004) Galanin and cognition. Behav Cogn Neurosci Rev 3:222–242
117. Fisone G, Wu CF, Consolo S, Nordstrom O, Brynne N, Bartfai T, Melander T, Hokfelt T (1987) Galanin inhibits acetylcholine release in the ventral hippocampus of the rat:

histochemical, autoradiographic, in vivo, and in vitro studies. Proc Natl Acad Sci USA 84:7339–7343
118. Holets VR, Hokfelt T, Rokaeus A, Terenius L, Goldstein M (1988) Locus coeruleus neurons in the rat containing neuropeptide, Y., tyrosine hydroxylase or galanin and their efferent projections to the spinal cord, cerebral cortex and hypothalamus. Neuroscience 24:893–906
119. Xu ZQ, Shi TJ, Hokfelt T (1998) Galanin/GMAP- and NPY-like immunoreactivities in locus coeruleus and noradrenergic nerve terminals in the hippocampal formation and cortex with notes on the galanin-R1 and -R2 receptors. J Comp Neurol 392:227–251
120. Melander T, Hokfelt T, Rokaeus A, Cuello AC, Oertel WH, Verhofstad A, Goldstein M (1986) Coexistence of galanin-like immunoreactivity with catecholamines, 5-hydroxytryptamine, GABA and neuropeptides in the rat CNS. J Neurosci 6:3640–3654
121. Xu ZQ, Hokfelt T (1997) Expression of galanin and nitric oxide synthase in subpopulations of serotonin neurons of the rat dorsal raphe nucleus. J Chem Neuroanat 13:169–187
122. Rodriguez-Puertas R, Nilsson S, Pascual J, Pazos A, Hokfelt T (1997) 125I-galanin binding sites in Alzheimer's disease, increases in hippocampal subfields and a decrease in the caudate nucleus. J Neurochem 68:1106–1113
123. Perez S, Basile M, Mash DC, Mufson EJ (2002) Galanin receptor over-expression within the amygdala in early Alzheimer's disease, an in vitro autoradiographic analysis. J Chem Neuroanat 24:109–116
124. Counts SE, Perez SE, Ginsberg SD, De Lacalle S, Mufson EJ (2003) Galanin in Alzheimer disease. Mol Interv 3:137–156
125. Baraban JM, Aghajanian GK (1980) Suppression of serotonergic neuronal firing by alpha-adrenoceptor antagonists: evidence against GABA mediation. Eur J Pharmacol 66:287–294
126. Baraban JM, Aghajanian GK (1980) Suppression of firing activity of 5-HT neurons in the dorsal raphe by alpha-adrenoceptor antagonists. Neuropharmacology 19:355–363
127. Quinaux N, Scuvee-Moreau J, Dresse A (1982) Inhibition of in vitro and ex vivo uptake of noradrenaline and 5-hydroxytryptamine by five antidepressants; correlation with reduction of spontaneous firing rate of central monoaminergic neurones. Naunyn Schmiedebergs Arch Pharmacol 319:66–70
128. Baraban JM, Aghajanian GK (1981) Noradrenergic innervation of serotonergic neurons in the dorsal raphe: demonstration by electron microscopic autoradiography. Brain Res 204:1–11
129. Yatham LN (2004) Newer anticonvulsants in the treatment of bipolar disorder. J Clin Psychiatry 65(suppl 10):28–35
130. Ettinger AB, Argoff CE (2007) Use of antiepileptic drugs for nonepileptic conditions: psychiatric disorders and chronic pain. Neurotherapeutics 4:75–83
131. Rada P, Avena NM, Leibowitz SF, Hoebel BG (2004) Ethanol intake is increased by injection of galanin in the paraventricular nucleus and reduced by a galanin antagonist. Alcohol 33:91–97
132. Lewis MJ, Johnson DF, Waldman D, Leibowitz SF, Hoebel BG (2004) Galanin microinjection in the third ventricle increases voluntary ethanol intake. Alcohol Clin Exp Res 28:1822–1828
133. Morilak DA, Cecchi M, Khoshbouei H (2003) Interactions of norepinephrine and galanin in the central amygdala and lateral bed nucleus of the stria terminalis modulate the behavioral response to acute stress. Life Sci 73:715–726
134. Gregersen S, Hermansen K, Langel U, Fisone G, Bartfai T, Ahren B (1991) Galanin-induced inhibition of insulin secretion from rat islets: effects of rat and pig galanin and galanin fragments and analogues. Eur J Pharmacol 203:111–114
135. Crawley JN, Austin MC, Fiske SM, Martin B, Consolo S, Berthold M, Langel U, Fisone G, Bartfai T (1990) Activity of centrally administered galanin fragments on stimulation of feeding behavior and on galanin receptor binding in the rat hypothalamus. J Neurosci 10:3695–3700
136. Schick RR, Samsami S, Zimmermann JP, Eberl T, Endres C, Schusdziarra V, Classen M (1993) Effect of galanin on food intake in rats: involvement of lateral and ventromedial hypothalamic sites. Am J Physiol 264:R355–R361

137. Kyrkouli SE, Stanley BG, Hutchinson R, Seirafi RD, Leibowitz SF (1990) Peptide-amine interactions in the hypothalamic paraventricular nucleus: analysis of galanin and neuropeptide Y in relation to feeding. Brain Res 521:185–191
138. Gundlach AL (2002) Galanin/GALP and galanin receptors: role in central control of feeding, body weight/obesity and reproduction? Eur J Pharmacol 440:255–268
139. Leibowitz SF (2005) Regulation and effects of hypothalamic galanin: relation to dietary fat, alcohol ingestion, circulating lipids and energy homeostasis. Neuropeptides 39:327–332
140. Tempel DL, Leibowitz KJ, Leibowitz SF (1988) Effects of PVN galanin on macronutrient selection. Peptides 9:309–314
141. Wiesenfeld-Hallin Z, Xu XJ (2001) Neuropeptides in neuropathic and inflammatory pain with special emphasis on cholecystokinin and galanin. Eur J Pharmacol 429:49–59
142. Zhang X, Ju G, Elde R, Hokfelt T (1993) Effect of peripheral nerve cut on neuropeptides in dorsal root ganglia and the spinal cord of monkey with special reference to galanin. J Neurocytol 22:342–381
143. Landry M, Aman K, Dostrovsky J, Lozano AM, Carlstedt T, Spenger C, Josephson A, Wiesenfeld-Hallin Z, Hokfelt T (2003) Galanin expression in adult human dorsal root ganglion neurons: initial observations. Neuroscience 117:795–809
144. Hua XY, Hayes CS, Hofer A, Fitzsimmons B, Kilk K, Langel U, Bartfai T, Yaksh TL (2004) Galanin acts at GalR1 receptors in spinal antinociception: synergy with morphine and AP-5. J Pharmacol Exp Ther 308:574–582
145. Amiranoff B, Servin AL, Rouyer-Fessard C, Couvineau A, Tatemoto K, Laburthe M (1987) Galanin receptors in a hamster pancreatic beta-cell tumor: identification and molecular characterization. Endocrinology 121:284–289
146. Lloyd RV, Scheithauer BW, Kovacs K, Roche PC (1996) The immunophenotype of pituitary adenomas. Endocr Pathol 7:145–150
147. Leung B, Iisma TP, Leung KC, Hort YJ, Turner J, Sheehy JP, Ho KK (2002) Galanin in human pituitary adenomas: frequency and clinical significance. Clin Endocrinol 56:397–403
148. Invitti C, Pecori Giraldi F, Dubini A, Moroni P, Losa M, Piccoletti R, Cavagnini F (1999) Galanin is released by adrenocorticotropin-secreting pituitary adenomas in vivo and in vitro. J Clin Endocrinol Metab 84:1351–1356
149. Hulting AL, Land T, Berthold M, Langel U, Hokfelt T, Bartfai T (1993) Galanin receptors from human pituitary tumors assayed with human galanin as ligand. Brain Res 625:173–176
150. Sethi T, Rozengurt E (1991) Galanin stimulates Ca2+ mobilization, inositol phosphate accumulation, and clonal growth in small cell lung cancer cells. Cancer Res 51:1674–1679