

Galanin, galanin receptors and drug targets

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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 ap-

proaches involving knockout animals. In the present review, 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. (Part of a Multi-author Review)

Keywords. Galanin receptor ligands, therapeutics, drug treatment, neuropeptides, G-protein-coupled receptors.

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 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 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 review.

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 [1–5] and upon seizure activity in the brain (reviewed in [6, 7]). Increased galanin concentrations appear to be neuroprotective [8–12] and to promote neurogenesis [11, 13–15]. 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 [14].

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 non-peptide 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

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Table 1. Distribution of galanin and the galanin receptor subtypes.

	CNS								Pancreas	Solid tumors
	BNST	Amygdala	Hippo- campus	Hypo- thalamus	DRN	Locus coeruleus	Spinal cord	DRG		
Galanin	+++	+++	+	+++	+	+++	++	++	+	++
GalR1	+++	+++	++	+++	++	+++	++	+++	+++	+++
GalR2	++	++	++	++	++	++	++	+++	++	++
GalR3	+/-	+/-	+/-	+	+/-	+/-	+/-	+/-	NA	NA
References	[13, 47, 48, 58, 70, 79, 84–99]								[57, 87, 100–106]	[73, 78–81, 107–111]

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	[17, 65, 112, 113]
Learning and memory	GalR1 and GalR2 in the hippocampus	[15, 24, 28, 114–116]
Seizure	GalR1 and GalR2 in the hippocampus	[7, 14, 15, 17, 19, 116–118]
Pain	GalR1 and GalR2 in the spinal cord and the DRG	[14, 69, 70, 79, 119, 120]
Anxiety and mood disorders	GalR1, GalR2 and GalR3 in the DRN, the hypothalamus, the locus coeruleus, the amygdala and BNST	[35, 49, 121–128]
Tumor	GalR1 and GalR2	[78, 79, 129, 130]

Table 3. Galanin receptor ligands as putative therapeutic targets.

Galanin receptor ligands	Various indicated therapeutic aspects	References
GalR1 Agonist	Analgesic, anticonvulsant, anxiolytic	[7, 14, 17, 19, 22, 69, 70, 118, 119, 122, 131, 132]
Antagonist	Antidepressant, cognitive enhancement, regulation of feeding	[14, 17, 23, 39, 40, 65, 123, 133, 134]
GalR2 Agonist	Analgesic, anticonvulsant, antidepressant, anxiolytic, neuroprotection/neuroregeneration	[2, 7, 11, 12, 15, 22, 35, 69, 70, 118, 120, 121, 123, 131, 132]
GalR3 Antagonist	Antidepressant, anxiolytic, block alcohol intake in addiction	[49–51, 55]

pharmacological experiments regarding the receptor subtype selective agonists.

Nevertheless, by combination of the results from transgenic animals null for specific galanin receptor subtypes and the use of the above-described agonists, it is now well established that both agonists and antagonists for the three galanin receptor subtypes can be used as putative therapeutic 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

[16], 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:

Table 4. Galanin receptor ligands in preclinical and clinical experiments.

Peptide type ligands				
Galanin	Non-selective agonist	i.v. (human), icv, intrathecally, locally into the brain area	Analgesic, anticonvulsant, antidepressant-, anxiolytic-like, attenuated LTP in DG Impaired cognition Inhibited glucose-stimulated insulin release	[25, 135-141]
Galanin (2–11)	GalR2/3 agonist	icv, intrathecally, locally into the brain area	Anticonvulsant-like, analgesic, neuroprotection	[69, 142, 143]
M35 M40	Non-selective antagonist	icv, intrathecally, locally into the brain area	Anxiolytic-like, Blocked the antidepressant-induced effect, induced a significant allodynic state in non-allodynic rats, blocked galanin-induced effects in feeding, cognition, seizure and depression model	[35, 125, 139, 144-146]
Non-peptide type ligands				
Galnon Galmic	GalR1/2 agonist	i.p.	Anticonvulsant, antidepressant-, anxiolytic-like, attenuated LTP in DG Stimulated insulin release	[15, 22, 25, 35, 83, 131, 147, 148]
*SNAP37889 *SNAP398299	GalR3 antagonist	p.o.	Antidepressant-, anxiolytic-like	[49, 149, 150]
3-(3,4-dichloro-phenylimino)-1-(6-methoxy-pyridin-3-yl)indolin-2-one	GalR3 antagonist	i.p.	Antidepressant-like	[50]

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

1. The GalR1 null mutation mouse has spontaneous seizures [17–19], 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 over-expression 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 [20, 21]. These experiments showed that pharmacologically applied of 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 non-selective agonists that are required for this action since galanin is a pan ligand for all three galanin receptor subtypes.

The pharmacological experiments using Galnon [22] and Galmic [14], 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 [23] 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) [24–27] and on various cognitive tasks [28, 29] showed that in normal young animals intra-hippocampal or icv 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 [30]. Galanin also coexists with noradrenaline [31–33] and serotonin [33–35] 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 dis-inhibit 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 better compensate the pathology by replacing more acetylcholine. 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 [36–38]. In particular, Mufson and his colleagues have shown that in Alzheimer's disease, the surviving cholinergic basal forebrain neurons were hyper-innervated by galaninergic fibers [39, 40]. One possibility would be, as suggested by these authors, that galanin hyper-innervation 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 [2, 10–12, 14]. 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) [31–33] and with serotonin in ca. 70 % of the serotonergic neurons in the dorsal raphe nucleus (DRN) [33–35]. 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 [41–44]. 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. (2005) 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 [45, 46].

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 [47, 48].

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 [49]. Another GalR3 selective antagonist was synthesized by Rebek and tested in antidepressant models [50], where it confirmed the findings by Swanson et al. (2005) 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 [51] and behavioral animal data [52, 53] have suggested that galanin action in the amygdala and elsewhere is involved in addictive behavior such as repeated alcohol intake [54]. 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 [55]. 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 [56].

The GalR1 receptor was first cloned from a human Bowes melanoma cell line and shortly after from a rat insulinoma cell line [57, 58]. Studies on pancreatic islets 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 [59–63], strongly induces feeding. The choice of food, if protein carbohydrates and fat are available, is directed towards fat preference [64]. Galanin is rapidly induced in the rat PVN (periventricular nucleus) upon fat intake [63]. 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 [65].

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 [66]. Nerve injury such as axotomy leads to a rapid induction of galanin expression in the sensory ganglia [4, 5, 67, 68]. Galanin has a biphasic response in many pain models, with low galanin doses (intrathecally) escalating and high doses suppressing pain [69, 70].

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 [71]. The GalR2-mediated depolarizing effects, while important for neuroregeneration, may contribute to pain sensation.

There is a strong effort ongoing 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 [72–79]. Clinical data were published on pancreatic tumor therapy, which now includes galanin in addition to the somatostatin receptor agonists octreotide and serotonin.

Small cell lung carcinoma and colon cancer isolates have also been shown to express galanin and GalR1 [57, 80] and in some cases GalR2 [81]. GalR2 signaling in small cell lung carcinomas has been studied in detail, and the influence of GalR2 on tumor growth has been shown [81, 82].

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 non-peptide 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. 6 million compounds at big pharmaceutical industry, no high-affinity (sub-micromolar affinity) and chemically workable (easy-to-develop analogs that have higher affinity with better pharmacological profile) compounds have yet been found.

The presently available non-peptide galanin receptor ligands are the GalR3 antagonists discovered by Synaptic-Lundbeck, which according the publication by Swanson et al. (2005), have high affinity (nanomolar) and high selectivity (50–100-fold over GalR1 and -2) [49]. These compounds exhibit antidepressant and anxiolytic efficacies in animal models.

The non-peptide galanin receptor agonists Galnon [22, 83] and Galmic [15] are micromolar to sub-micromolar affinity and are not selective between GalR1 and GalR2 receptors. In the therapeutic indication of epilepsy, a non-selective GalR1/GalR2 agonist is advantageous, as GalR1 and GalR2 signaling suppress the initiation and maintenance of seizures, respectively [7]. 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 to the galanin receptor subtypes will be found, because the biological data are compelling for their therapeutic benefits.

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