

Galanin Receptors

Key References

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Overview

Galanin is a 30 amino acid non-amidated peptide in humans and identified in 14 other species as a 29 amino acid C-terminally amidated peptide. Galanin is widely distributed in both the central and peripheral nervous systems and the endocrine system. Galanin's wide spectrum of biological activities makes the galaninergic system a promising target for possible therapeutic intervention in pain signaling, cognitive decline, neuroprotection, feeding behavior and controlling insulin release. Galanin affects the release and postsynaptic action of classical neurotransmitters like acetylcholine, norepinephrine, serotonin and dopamine. Galanin co-exists with other neuropeptides, like neuropeptide Y, substance P and vasoactive intestinal peptide, and has been shown to modulate their release and activity. In addition to these actions galanin has more recently been shown to play a trophic and cell survival role to both central and peripheral neurons, implying a role in stroke, brain injury/disease and peripheral neuropathy.

Galanin is a strongly inhibitory, hyperpolarizing peptide, which reduces the excitability of its target cells. Galanin, acting at the three galanin receptors, opens ATP-sensitive potassium channels, closes calcium channels (N- and L-types), modifies intracellular calcium levels, reduces the stimulatory effect of muscarinic agonists on phospholipase C and modulates the activity of adenylyl cyclase.

Transgenic mice with a disrupted or overexpressing galanin gene have been generated (GalKO, GalOE, respectively). Abnormalities in lactation, pituitary responsiveness to estrogen, and peripheral nerve injury, as well as an increased ability to develop status epilepticus have been described in galanin

deficient animals. Animals overexpressing galanin in the central and/or peripheral nervous systems demonstrate suppression of nociception and neuropathic pain behavior, seizure development, a reduction in hippocampal cell death after excitotoxic damage as well as suppressed hippocampal excitability and cognitive deficits. The diverse physiological effects of galanin are mediated via three G protein-coupled receptors referred to GalR1-3, which have been cloned from several species (human, rat, mouse), showing only 40-60% amino acid identity.

GalR1 is localized mainly in the hypothalamus, the hippocampus and the spinal cord, and is negatively coupled to adenylyl cyclase through G_i/G_o proteins. GalR2 has been cloned from rat hypothalamus, rat dorsal root ganglia, human placenta, human DNA library and from mouse brain; Unlike GalR1 and GalR3, GalR2 positively couples to phospholipase C mediated via G_{q/11} and hence activates the MAP kinase pathways (ERK). It is activated by galanin (2-11), galanin (2-29) and [D-Trp²]-galanin. GalR3 was cloned from rat hypothalamus and is localized mainly in the heart, spleen and testis; it recognizes galanin (2-29) as specific ligand. GalR3 couples to G_i/G_o proteins and mediates opening of G protein-coupled inward-rectifying potassium channels (GIRK).

Several peptide type chimeric galanin receptor ligands, M15 (Galantide), M32, M35, M40 and C7, have been synthesized. These can act as galanin receptor antagonists in numerous situations *in vivo* although their detailed pharmacology is as yet poorly understood. Further, these chimeric ligands act often as full or partial agonists *in vitro* to all three galanin

receptors when expressed in various stably transfected cell lines.

Five types of low MW galanin receptor ligands have been reported. A fungal metabolite SCH-202596 (IC₅₀ of 1.7 μM at hGalR1), a series of dithiin-1,1,4,4-tetroxide derivatives that are GalR1 antagonists with submicromolar affinity; galnon, a low molecular weight tripeptidomimetic agonist (K_i of 3-8 μM), which is equally active against all three receptor subtypes and is systemically active and affects appetite, seizures and pain; and galmic, identified from a small synthetic scaffold library with a K_i = 34.2 μM for GalR1. Galmic suppresses long-term potentiation in the dentate gyrus; blocks status epilepticus (i.hc or i.p.); shows antidepressant-like effects in the forced-swim test (i.p.), and it is a potent inhibitor of flinching behavior in the inflammatory pain model induced by formalin injection. Finally, N⁴-[3-(benzyloxy)phenyl]-2-[4-(2-fluorophenyl)-1-piperazinyl]-N⁶,N⁶-dimethyl-4,6-pyrimidinediamine has been reported as a 20 nM GalR3 specific ligand with antidepressant activity.

Galanin-Like Peptide, GALP, a 60 amino acid neuropeptide isolated from porcine hypothalamus contains the non-variable 1-13 amino acids of galanin between positions 9 and 21. GALP binds GALR1 and GalR2 but neither receptor is thought to mediate the endogenous actions of GALP since the peptide retains biological activity in GalR1 or GalR2 knock-out animals. A GALP-specific receptor has yet to be identified.

Galanin Receptors

CURRENTLY ACCEPTED NAME	GalR1	GalR2	GalR3
ALTERNATIVE NAME	Galanin receptor type 1	Galanin receptor type 2	Galanin receptor type 3
STRUCTURAL INFORMATION	349 aa (human)	372 aa (rat)	370 aa (rat)
AGONISTS	Galanin (G0278 (h), G5773 (p), G8272 (r)), Galanin (G0278 (h), G5773 (p), G8272 (r)) Galanin (1-16) (G112), GALP (G8041), Galnon, galmic	Galanin (G0278 (h), G5773 (p), G8272 (r)), Galanin (2-16), Galanin (2-11) (G8293 (p,r)), GALP (G8041)	Galanin (G0278 (h), G5773 (p), G8272 (r)), Galanin(2-29), N ⁴ -[3-(Benzyloxy)phenyl]-2-[4-(2-fluorophenyl)-1-piperazinyl]-N ⁶ ,N ⁶ -dimethyl-4,6-pyrimidinediamine
ANTAGONISTS	M15 (Galantide) (G1278), M35, M40 (G7285), C7 (G7160), M32 (G8165), [D-Thr ⁶ ,D-Trp ^{8,9}](1-15)ol Galanin(1-15)ol fragment 1-15 (G3535), [D-Trp ^{8,9}]-Galanin(1-15)ol, SCH-202596, Dithiin-1,1,4,4-tetroxide	M15 (Galantide) (G1278), M35, M40 (G7285), C7 (G7160), M32 (G8165), [D-Thr ⁶ ,D-Trp ^{8,9}](1-15)ol Galanin fragment 1-15 (G3535), D-Thr ⁶ ,D-Trp ^{8,9} -Galanin(1-15)ol (G 3535) [D-Trp ^{8,9}]-Galanin(1-15)ol	M15 (Galantide) (G1278), M35, M40 (G7285), C7 (G7160), M32 (G8165), [D-Thr ⁶ ,D-Trp ^{8,9}](1-15)ol Galanin fragment 1-15 (G3535), D-Thr ⁶ ,D-Trp ^{8,9} -Galanin(1-15)ol (G3535) [D-Trp ^{8,9}]-Galanin(1-15)ol
SIGNAL TRANSDUCTION MECHANISMS	G _{i/o} (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG)	G _{i/o} (GIRK modulation)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-Galanin, porcine, human, rat	[¹²⁵ I]-Galanin, porcine, human, rat	[¹²⁵ I]-Galanin, porcine, human, rat
TISSUE EXPRESSION	Hypothalamus, amygdala, hippocampus, thalamus brainstem, spinal cord, DRG, heart, lung, kidney and testis	Cortex, hypothalamus, hippocampus, amygdala, cerebellum, DRG, heart, liver, lung, kidney, intestine, uterus, ovary, stomach, pancreas, testis	Hypothalamus, pituitary, cerebral cortex, medulla, cerebellum, olfactory bulb, spinal cord, heart, spleen, testis, liver, kidney, stomach, lung, DRG
PHYSIOLOGICAL FUNCTION ^a	Glu ↓, NE ↑, 5-HT ↑↓, SP release ↓ cholinergic neuron survival ↑, Ach ↑↓ insulin release ↓	Cholinergic neuron survival ↑, Ach ↑ ↓, NE ↑ GH ↑ modification of leptin, NPY, DA response	GH ↑ modification of leptin, NPY, DA response
DISEASE RELEVANCE ^a	Anticonvulsant, ischemia, antidepressant, analgesia, allodynia, Alzheimer's disease, cognitive enhancer	Alzheimer's disease, cognitive enhancer, Dwarfism, feeding disorders, anticonvulsant, antidepressant, neuroprotection	Dwarfism, feeding disorders, depression, antidepressant

Abbreviations

Ach: Acetylcholine

C7: Galanin (1-13)-spantide amide

DA: Dopamine

DRG: Dorsal root ganglion

GALP: Galanin-Like Peptide

GH: Growth hormone

Glu: Glutamate

5-HT: Serotonin

M15: Galanin (1-13)-substance P (5-11) amide

M32: Galanin (1-13)-neuropeptide Y (25-36) amide

M35: Galanin (1-13)-bradykinin (2-9) amide

M40: Galanin (1-13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala amide

NPY: Neuropeptide Y

SCH-202596: Spirocoumaranon

SP: Substance P

h: human,

p: porcine,

r: rat

FOOTNOTES

^a Disease relevance overlaps between GalR subtypes.