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NEUROPEPTIDE GALANIN IN HEALTH AND DISEASE: A REVIEW

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ABSTRACT

Galanin is a regulatory neuropeptide, widely distributed in the nervous system and gut, that acts via three subtypes of G protein-coupled receptors, named galanin receptor 1 (GAL-R1), GAL-R2 and GAL-R3. Galanin and its receptors are expressed in the hypothalamic paraventricular and supraoptic nuclei, anterior pituitary and adrenal medulla. Galanin is widely expressed in the central and peripheral nervous system, endocrine system and co-exists with a number of classical neurotransmitters. Galanin mediates widespread about partially overlapping distribution in the brain, and by partially different transduction mechanisms. The GAL-R1 is coupled to Gi/Go types of G-proteins and mediates inhibitory actions of galanin, GAL-R3 is coupled to Gi/Go-proteins and mediates a hyperpolarization response. The GAL-R2, mainly mediates stimulatory effects of galanin on neurotransmitter release, since it is coupled to the phospholipase C pathway, intracellular Ca2+ mobilization and Ca2+-dependent Cl– channel activation. Galanin is involved in the control of feeding, alcohol intake, seizure threshold, cognitive performance and control of pain threshold. This review aims to summarize the current data of the importance of the galanin and galanin

receptor subtypes and their involvement in different physiological and pathological functions.

KEYWORDS: (3-6 words): Galanin, Neuropeptide, G protein-coupled receptor, Hypothalamus.

INTRODUCTION

Galanin (GAL) is one of the most inducible neuropeptide,[1] with 29–30 amino acids that is widely distributed in the brain, including the paraventricular nucleus of hypothalamus,[2,3] Its biosynthesis is increased 2–10 fold upon axotomy in the periphery.[4,5] and upon seizure activity in the brain.[6,7] By central mechanisms, it is involved in the control of feeding, alcohol intake, seizure threshold, cognitive performance and mood, and through peripheral mechanisms in the control of pain threshold.[9] Three galanin receptor (GalR) subtypes, GalR1 and GalR2 are found in many regions of the central nervous system (CNS) as demonstrated with in situ hybridization, radioligand binding, and immunohistochemical studies all with a high affinity for galanin. GalR1–3, has been cloned and belong to the rhodopsin sub- family of G protein-coupled receptor (GPCR's),[7-9] GalR1 and GalR3 are coupled to Gi/o leading to inhibition of adenylate cyclase, increase in mitogen-activated protein kinase (MAPK) activity and opening of G protein-coupled inwardly rectifying K+ channels. GalR2 is coupled to Gq/11 and its activation leads to increase in phospholipase C with formation of inositol triphosphate (IP3) increasing intracellular calcium levels and of diacylglycerol (DAC) with the subsequent activation of the protein kinase C^9. This review serves to summarize the indications that GAL-R subtypes may form heteromers with each other and other types of GPCRs in the CNS as a molecular mechanism to modulate the function of different types of glianeuronal networks.

DEPRESSION

Major depressive disorder (MDD) is a common and debilitating condition with pervasive impact on the quality of life for both patients and their families,[10] It is estimated that 10% to 15% of the general population experience clinical depression during their lifetime. MDD is twice as common in women as in men,[11,12] and is associated with a high morbidity rate,constituting a significant worldwide health burden. The etiology of MDD is not fully understood, it is recognized that genetic, environmental, psychological and social factors all contribute to the pathogenesis of depression.[14,15] Family, twin, and adoption studies indicate that genetic factors play a particularly important role in the development of MDD.[16,17] Twin

studies suggested that the heritability of MDD is 40% to 50%, while family studies indicate that the first-degree relatives of MDD patients have a two to three-fold increase in the lifetime risk of developing the disorder.[18] These studies make it possible to identify genes of substantial influence on MDD risk through molecular genetic techniques. Both animal and human studies have demonstrated that galanin, which are widely expressed in the brain, spinal cord and gut, possesses a potent antidepressant activity.[19] This implies that the GAL gene may be involved in the development of MDD. A study done by Yong-Jun Wangs showed a significant correlation between GAL gene polymorphisms of rs694066 and the susceptibility of MDD, this correlation was gender-dependent: a positive correlation between GAL SNPs and the incidence of MDD was observed only in female patients but not in male patients. Recent studies have demonstrated that much more women than men suffered MDD,[13,20] This difference may be related to the difference in GAL gene polymorphisms between male and female patients. The GAL gene polymorphism site of rs948854 showed a high degree of correlation with the severity of symptoms of female patients with depression.[21,22] suggesting a positive correlation between the GAL gene polymorphism and the susceptibility of female patients to depression. The release disturbance of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) might be associated with an increased susceptibility to depression.[23-25] There are direct and indirect evidences suggesting that GAL plays a regulatory role in the MDD- associated disorder of 5-HT and NE,[26,27] GAL significantly inhibits the stimulation-evoked NE release in a dose dependent manner.[28] and exerts an inhibitory effect via increasing the K+ conductance in serotonergic dorsal raphe neurons and noradrenergic locus ceruleus (LC) neurons by acting on a postsynaptic receptor.[29,30]

ALZIEHMER'S DISEASE

GAL and its cognate G protein-coupled receptors (GALR1–3) are widely distributed in the mammalian CNS and modulate several ascending neurotransmitter systems including cholinergic, noradrenergic, serotonergic as well as neuroendocrine pathways.[31,32] Galanin activity regulates cognitive behaviors mediated by the basal fore-brain, amygdala, hippocampus, and entorhinal cortex.[33,34] cholinergic basal forebrain (CBF) neurons that provide the major cholinergic innervation to the cortex and hippocampus,[35] and plays a keyrole in memory and attention functions.[36] CBF neurons undergo selective degeneration during later stages of Alzheimer's disease (AD), which correlates with disease duration and degree of cognitive impairment.[37] Galanin levels increase throughout the cortex in AD,[38,39]

and GALR binding sites are amplified in the cortex, CBF, hippocampus, entorhinal cortex, and amygdala during the course of the disease.[40,41] Galanin upregulation may promote cholinergic neuronal survival in late-stage AD, and gene expression profiling of individual CBF neurons in AD tissue suggests that galanin hyperinnervation positively regulates mRNAs that promote cholinergic neuron function and survival.[42-44]

STRESS

Galanin decreases the severity of morphine withdrawal symptoms through the activation of GalR1 receptors located in the LC.[45] Increased activity of LC neurons may be responsible for many of the symptoms observed after withdrawal from morphine, and naloxone precipitated morphine withdrawal enhances the activity of the HPA axis.[46] Noradrenergic LC neurons send projections to the PVN, these cells also release galanin into the hypothalamic nuclei.[47,48] Central administration of galanin reduces stress related responses through GalR1 receptors.[49] it is possible that the ability of galanin to alleviate morphine withdrawal signs is mediated, through activation of GalR1 receptor, which in turn inhibits noradrenergic neurons in the LC that project to the PVN in the hypothalamus.[50]

FEEDING BEHAVIOUR

Galanin actions on circulating hormones related to appetite and body weight is well documented, such as inhibition of insulin secretion and stimulation of growth hormone release,[51,52] It induces ingestion of increased quantities of food with preference for fat.[53,54] and the presence of substantial fat in the body's system elicits increased response to galanin and may enhance fat deposition through a reduction in energy expenditure.[53] Galanin microinjected into the paraventricular nucleus of the hypothalamus and central amygdala drastically increased food intake,[55] In women with anorexia nervosa, it is possible that reduced galanin expression, as manifest by low CSF levels, may contribute to food avoidance and perhaps aversion to fat. Galanin is not strongly responsive to food deprivation or to changes in leptin is therefore apparently not a primary response peptide to food scarcity. Thus, galanin seems to stimulate, in a non- homeostatic manner, the consumption of foods that would promote weight gain rather than meeting short-term metabolic needs.[53]

TUMOUR SUPPRESSOR

Galanin has tumor suppressor activity and is frequently inactivated by aberrant promoter methylation in head and neck cancer.[56,57] Antibody blockade of GALR1 enhances proliferation of Head and neck squamous cell carcinoma (HNSCC) cells.[56] and galanin and

GALR1 induce a marked and prolonged extracellular signal regulated kinase (ERK)1/2 activation, up-regulation of p27Kip1 and p57Kip2, down-regulation of cyclin D1, and consequent inhibition of cell proliferation.[58]

VASOVAGAL SYNCOPE

Galanin is present within the central and peripheral nervous system, especially cardiac sympathetic neurons.[59] It takes part in the regulation of cardiovascular homeostasis,[60] and lowers norepinephrine plasma levels, thus attenuate blood pressure response to orthostasis.[61] They inhibit acetylcholine, glutamate, and insulin release, stimulation of feeding, stimulation of pituitary hormone release, and inhibition of spinal nociceptive reflexes.[62]

REPRODUCTION

Galanin stimulates GnRH release, whereas galanin antagonists[63,64] and antiserum.[65] block the LH surge and ovulation and secreted in a pulsatile manner,[66,67] Galanin receptors on GnRH neurons have been detected,[68] and a subset of GnRH neurons expresses galanin.[69,70] Galanin action at these neurons in a paracrine/autocrine system may be part of the process by which the GnRH pulse shape is formed.[71] Galanin is markedly up-regulated by estrogen.[72-74] via estrogen beta receptors,[75] in galanin neurons and levels peak in GnRH neurons.[76,77] Thus, galanin has bipolar activity, such that at some stages of the cycle when estradiol levels are low it can be inhibitory.[78]

COLON CANCER

Galanin's functions in the GI tract include inhibition of gastric acid secretion and inhibition of the release of pancreatic peptides such as insulin, amylase, glucagon and somatostatin.GalR1 is the predominantly expressed galanin receptor in the human colon. Different signal transduction pathways associated with each galanin receptor may account for distinct biological activities of galanin in different types and possibly different stages of cancer,[79] Clinically, galanin mRNA was found to be overexpressed in colorectal tumours, high galanin mRNA expression correlated with poor disease free survival in early stage disease. GalR1 of cancer-promoting properties is known to signal through the MAPK pathway, and mitogenic effects of galanin have been reported in pancreatic cancer cells,[80] small cell lung cancer cells.[81] and rat pituitary tumour cells in vitro.[82] GalR1 has been implicated as a tumour suppressor since loss of the GALR1 locus, 18q23, have been reported in HNSCC.[83] and metastatic colorectal cancer,[79,84] Galanin is considered to be a marker of pluripotent stem cells. Four of the most significantly over-expressed genes in undifferentiated

embryonic tissue are galanin, POU5F1, NANOG and DPPA4.[85,86] with galanin highlighted as the most abundantly expressed in human and rodent embryonic stem cells (ESCs),[85,87] Up-regulation of galanin mRNA and protein expression has been reported in undifferentiated embryonal carcinoma, suggesting a diagnostic marker for undifferentiated tumour cells.[88] Therefore, galanin with stem cell like properties is linked to the novel role in mediating chemotherapy resistance in colorectal cancer.

EPILEPSY

Galanin is released during epileptic seizures and has an inhibitory effect on neuronal activity through presynaptic inhibition of glutamatergic transmission, as well as a strong neuroprotective effect.[89] In a study by Lin and colleagues (2003), an rAAV constitutively overexpressing preprogalanin was injected into the rat hippocampus. Kainic acid-induced seizure activity was significantly decreased, confirming the antiepileptic effect of galanin in vivo.[90] Administration of rAAV-preprogalanin resulted in long lasting expression of galanin, but also in the transport of the neuropeptide along the axonal arborization. Preinfusion of AAV-FIB-galanin into the inferior collicular column increased the threshold for seizures. Following infusion into the hippocampus, AAV-FIB-galanin resulted in suppression of electrographic and behavioral seizures induced by kainic acid and also had a neuroprotective effect on the survival of hilar interneurons.[91]

PAIN SYNDROMES

Galanin is expressed in both sensory and spinal cord interneurons and plays a key role in pain signaling,[92] Nerve injury such as axotomy leads to a rapid induction of galanin expression in the sensory ganglia.[93-96] Galanin has a biphasic response in many pain models, with low galanin doses (intrathecally) escalating and high doses suppressing pain,[97,98] 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,[99] The GalR2-mediated depolarizing effects, while important for neuroregeneration, contributes to pain sensation. Thus, there is a strong effort in progress to find GalR1 agonists for systemic or intrathecal use in pain therapy.

ALCOHOL INTAKE

Studies done on human,[100] and animal.[101,102] have suggested that galanin action in the amygdala, is involved in addictive behavior such as repeated alcohol intake.[103] Study done

by Befler et al showed that GalR3 had 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.[104] Therefore, development of galanin receptor antagonists, in particular GalR3 antagonists, might be a breakthrough in the addiction relevant field.

LUNG CARCINOMA

Multiple neuropeptides are screened for their ability to induce a rapid increase in [Ca2+] in different SCLC cell lines. Ca2+ mobilization is one of the components of a complex array of signaling events rather than the signal that promotes cell growth. Bradykinin, cholecystokinin, galanin, neurotensin, and vasopressin induce a rapid and transient increase in [Ca2+] in SCLC cell lines. These neuropeptides increased [Ca2+] in a dose-dependent fashion in the nanomolar range,[105,106] In pancreatic cells galanin activates an ATP-sensitive K+channel, hyperpolarizes the plasma membrane, and inhibits the activity of voltage-dependent Ca2+ channels.[107] In this manner it reduces Ca2+ influx and blocks the activity of various agents that increase the intracellular concentration of Ca2+. Surprisingly, in SCLC cell lines galanin caused a rapid and transient increase in [Ca2+],[105] Recent studies showed that galanin induced rapid mobilization of Ca2+ from internal stores and stimulated early production of inositol phosphates.[106] Thus, these studies suggest that SCLC express a novel type of galanin receptors that are coupled to Ca2+ mobilization.

FLUID INTAKE RGULATION

Galanin coexists with vasopressin in the hypothalamus.[108] It inhibits the release of vasopressin under various conditions of osmotic challenge, when vasopressin release is maximal,[109-111] Further, experimental manipulations producing hyperosmosis and hypovolemia upregulated galanin and GalR1 mRNA in magnocellular paraventricular nucleus of the hypothamaus,[112-118] A recent study has demonstrated galanin inhibition of angiotensin II-sensitive neurons in the subfornical organ, a brain structure thought to be critical to integrating osmotic and hypovolemic thirst messages and then activating behavior directed toward water seeking.[119]

CONCLUSION

The role of neuropeptides and their multiple receptors systems is still a more or less unexplored area in disturbances related to different pathologies. Galanin is a neuropeptide widely distributed in the nervous system, is involved in anti-depressent activity, cognitive function, increase apetite, tumour suppressor activity, GnRH release, regulation of

cardiovascular homeostasis, decrease the severity of morphine withdrawal symptoms, inhibition of gastric acid secretion, inhibition of release of pancreatic peptides, inhibition of release of vasopressin, inhibitory effect on neuronal activity, addivtive behavior and a key role in pain signaling. Detailing the role of the neuropeptides in brain plasticity during normal and pathological conditions is a prerequisite for further progress. A major drawback is the limited knowledge of the molecular and neurochemical changes underlying and also critical to develop better animal models, to study neuropeptide expression with its receptors that integrates information in pathological states.

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