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Galanin impairs cognitive abilities in rodents: relevance to Alzheimer's Disease

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Abstract. The neuropeptide galanin and its receptors are localized in brain pathways mediating learning and memory. Central microinjection of galanin impairs performance of a variety of cognitive tasks in rats. Transgenic mice overexpressing galanin display deficits in some learning and memory tests. The inhibitory role of galanin in cognitive processes, taken together with the overexpression of galanin in Alzheimer's disease, suggests that galanin antagonists may offer a novel therapeutic approach to treat memory loss in Alzheimer's patients. (Part of a Multi-author Review)

Keywords. Alzheimer's, fear conditioning, learning and memory, Morris water maze, receptor knockout mice, social transmission of food preference, transgenic mice.

Introduction

The discovery of galanin overexpression in the basal forebrain in Alzheimer's disease prompted investigations into the role of galanin in cognitive functions. Galanin fibers and terminals hyperinnervate the remaining cholinergic neurons of the nucleus basalis of Meynert in middle to advanced stages of Alzheimer's [1 – 5]. Further, galanin receptor densities in the nucleus basalis and amygdala nuclei differ from age-matched controls at specific stages of Alzheimer's disease progression [6 – 8]. These clinical findings prompted the hypothesis that galanin plays a role in the memory decline that is the primary behavioral symptom of Alzheimer's disease.

To test the role of galanin in memory, galanin was administered centrally to rats. Impairments in performance were detected on multiple learning and memory tasks. Acquisition of the conventional Morris water maze task, a starburst radial maze spatial task, passive avoidance, and trace cued fear conditioning were blocked by pharmacological doses of galanin, administered before training trials [9 – 14]. Working memory on T-maze delayed alternation and operant non-matching to position working memory tasks were impaired by galanin pretreatment [15 – 22]. Memory consolidation after Morris water maze training was prevented by galanin administration 30 min after the training trials [23]. Further, galanin decreased long-term potentiation in rat and guinea pig hippocampal slices through inhibition of cholinergic Schaffer collaterals, relevant to synaptic plasticity involved in learning [24, 25].

The contribution of endogenous galanin was investigated in rats using galanin receptor antagonist treatments. Three galanin receptor subtypes have been identified to date [26 – 28]. Peptidergic sequences and non-peptidergic compounds with moderate selectivity for each of the three subtypes have been developed [27 – 29]. Administration of the peptidergic galanin receptor ligand M40 alone did not alter performance in normal rats on delayed nonmatching to position, although M40 blocked the inhibitory actions of galanin in this operant working memory task [21]. M40 potentiated the beneficial actions of a cholinergic agonist in cholinergically lesioned rats on delayed non-matching to position [30]. The peptidergic galanin receptor ligand M35 facilitated spatial learning in the Morris water maze when given alone in one unreplicated study [31].

The contribution of endogenous galanin to cognitive processes was further investigated in mice with targeted mutations in the galanin gene. Two lines of transgenic mice overexpressing the galanin gene, one on a dopamine β-hydroxylase promoter (DβH), that confers specificity to adrenergic neurons [32, 33], and one on a platelet-derived growth factor promoter (PDGF) with a more widespread distribution in the brain [34–37]. Both have been tested on cognitive tasks. Galanin-overexpressing mice with the transgene on the DβH promoter displayed deficits on the more difficult components of several learning and memory tasks, including failing the probe trial test on the Morris water maze, impaired learning of social transmission of food preference and reduced fear conditioned freezing on the more challenging trace fear conditioning task [14, 32, 38–40]. In contrast, the DβH galanin transgenic mice were not different from their wildtype littermates on number of days to reach criterion on acquisition of the Morris water maze and an operant appetitive task, and were normal on attentional mechanisms in the 5-choice serial reaction time task [32, 41, 42]. Galanin-overexpressing transgenic mice with the transgene on the PDGF promoter displayed acquisition curves and selective quadrant search in the probe trial that did not differ from wildtype controls [37]. However, when tested during old age, at 19 months, the PDGF galanin transgenic mice were slower to learn the location of the hidden platform training on the Morris water maze task, spent less time in the trained quadrant during the delayed probe trial and displayed more thigmotaxis, while swim speeds did not differ between genotypes [43]. Conversely, galanin null mutant mice deficient in the galanin gene and galanin peptide also displayed a small deficit on the Morris water maze at older ages, and on a spatial object recognition task, indicating that too little galanin may also have deleterious consequences on cognition, perhaps related to the effects of galanin at early developmental stages [41, 44].

A critical question in therapeutic development is which receptor subtype to target. In the absence of highly selective galanin receptor subtype antagonists that are soluble in vehicles appropriate for behavioral studies, knockout mice with targeted mutations in galanin receptor genes offer an opportunity to evaluate the individual contributions of the GalR1, GalR2 and GalR3 receptor subtypes in cognitive functions. Galanin receptor knockout mice with conventional mutations in the GalR1 and GalR2 receptor subtypes have been tested on several learning and memory tasks. GalR1 null mutants were not significantly different than wildtype littermates on Morris water maze acquisition and probe trial performance, social transmission of food preference, standard delay fear conditioned freezing or trace fear conditioned freezing [40, 45]. GalR2 null mutants were not significantly different than wildtype littermates on the Morris water maze, standard delay contextual fear conditioning, or trace contextual and cued fear conditioning [46, 47].

The lack of significant effects on learning and memory of galanin antagonist treatment in rats, and galanin receptor mutation in mice, argues against a strong role for endogenous galanin under baseline physiological conditions in normal learning and memory processes. One explanation is the frequency coding hypothesis for neuropeptide release. Higher frequencies of neuronal firing are required to release peptide transmitters than to release small-molecule classical transmitters such as glutamate and acetylcholine [48–51]. Standard learning and memory tasks may not activate neuronal firing to levels sufficient to release endogenous galanin. Galanin may be released only under extreme physiological conditions, and therefore exert its inhibitory effects on cognitive tasks only during very demanding behavioral tasks [52, 53]. In the human brain, galanin may be released and exert its inhibitory effects similarly only under unusual physiological conditions, such as during the progression of neurodegeneration in Alzheimer's disease, when high levels of galanin overexpression appear [5, 53, 54]. The frequency coding interpretation is supported by findings from the nociceptive flexor reflex in galanin-overexpressing transgenic mice, which display a lower magnitude of central sensitization during repeated stimulation of c-fibers, although the wind-up effect did not differ from wildtype controls [55]. Further, while GalR1 null mutants did not differ from wildtype at baseline on most nociceptive measures of baseline mechanical and heat sensitivity, GalR1 null mutants showed longer durations of pain-like behaviors after partial lesion of the sciatic nerve [56]. These findings support an interpretation of inhibitory actions of galanin on spinally mediate pain, but only when the system is perturbed [57]. Further, the inhibitory actions of galanin on the release of other neurotransmitters, including acetylcholine and glutamate [20, 49, 51, 58–60], is greater in the DβH galanin transgenic mice than wildtype controls, primarily under conditions of high stimulation [51, 60]. Consequently, the DβH galanin-overexpressing transgenic mice were more resistant to seizures than wildtype controls, indicating inhibitory effects of endogenous galanin only when the hippocampus is highly activated [51, 61].

Another likely explanation is that galanin modulates cognitive functions through more than one of its three receptor subtypes. All three galanin receptors are members of the G-protein-coupled family of receptors

Table 1. Pharmacological and endogenous actions of galanin in rodent learning and memory tasks.

A) Central administration of galanin to rats Task	Effect on cognition	Reference
Morris water task		
	Slower acquisition curve	[9]
	No effect	[75]
	Slower acquisition with no change in retention	[22]
	Deficit in acquisition (strain-dependent)	[12]
	Deficit in consolidation	[23]
Starburst radial maze		
	Deficit in acquisition	[10]
T-maze delayed alternation		
	Reduction in choice accuracy	[16]
	Inhibition of acetylcholine induced improvement after cholinergic lesion	[15]
Spontaneous alternation		
	Decrease in choice accuracy	[76]
Passive avoidance		
	Decrease in step-down latency	[11]
Active avoidance		
	Decrease in avoidance responses during retention and extinction trials	[77]
Delayed nonmatching to position		
	Decrease in choice accuracy	[17, 19]
	Potentiation of scopolamine-induced reduction in choice accuracy	[18]
	Decrease in choice accuracy blocked by M40	[21]
	Potentiation of decrease in choice accuracy after cholinergic lesion	[78]
	Potentiation of M1 agonist improvement after cholinergic lesion	[30]
B) Targeted gene Mutations in galanin and its receptors. Mutation	Effect on cognition	Reference
Galanin-overexpressing transgenic mice		
GAL-tg (DβH promoter)	Impaired on Morris water maze probe trial	[32]
GAL-tg (DβH promoter)	Impaired on trace fear conditioning	[14]
GAL-tg (DβH promoter)	Impaired on social transmission of food preference	[39]
GAL-tg (PDPF promoter)	Normal at young age on Morris water maze acquisition	[37]
GAL-tg (PDPF promoter)	Impaired at old age on Morris water maze acquisiton	[43]
Galanin peptide knockout mice		
GAL null mutant	Impaired at older age on Morris water maze acquisition	[44]
GAL null mutant	Impaired on spatial object recognition	[41]
Galanin receptor knockout mice		
GAL-R1 null mutant	Normal on Morris water maze	[45]
GAL-R1 null mutant	Normal on social transmission of food preference	[45]
GAL-R1 null mutant	Impaired on trace cued fear conditioning	[45]
GAL-R2 null mutant	Normal on Morris water maze	[47]
GAL-R2 null mutant	Normal on trace contextual and cued fear conditioning	[47]

with conventional seven transmembrane spanning regions, and linked to an inhibitory G-protein and cyclic-AMP signal transduction cascade [26–28, 62, 63], However, GalR1 and GalR3 inhibit adenylate cyclase through a G_i pathway, while GalR2 acts at G_o, G_q, and G_i [27, 28, 63]. In addition, the anatomical distributions of each subtype differ across brain regions [64, 65]. Understanding the biological actions of each galanin receptor subtype, and the interplay between them, may be necessary to effectively

manipulate GalR1, GalR2 and GalR3 neurotransmission toward improving cognitive function. Thirdly, galanin has effects on anxiety-related behaviors, depression-related behaviors and stress-related responses [29, 42, 47, 66–70]. Stress and related behaviors may indirectly or directly influence cognitive performance.

Actions of galanin in animal models have raised the possibility of novel galaninergic therapeutics for Alzheimer's, depression, neuropathic pain, drug abuse and epilepsy [53, 54, 57, 65, 69, 71–73]. A large and growing literature provides evidence that galanin inhibits the release of other neurotransmitters and inhibits signal transduction mechanisms common to many neurotransmitters [20, 28, 49, 52, 54, 58, 73]. The inhibitory neuromodulatory actions of galanin in many neuroanataomical pathways [74] encourages the development of galaninergic drugs as an adjunct to existing neuropharmacological treatments [28]. Combinations of a galaninergic compound with a cholinergic, glutamatergic, GABAergic, serotonergic or noradrenergic drug may enhance the clinical efficacy of available treatments and/or enable the use of combinations of lower doses of each drug to obtain the maximal therapeutic benefit.

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