Galanin and Epilepsy: Promises with Nuances. . .

Patterns of Seizures, Hippocampal Injury, and Neurogenesis in Three Models of Status Epilepticus in Galanin Receptor Type 1 (GalR1) Knockout Mice

Mazarati A, Lu X, Shinmei S, Badie-Mahdavi H, Bartfai T

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The neuropeptide galanin exhibits anticonvulsant effects in experimental epilepsy. Two galanin-receptor subtypes, GalR1 and GalR2, are present in the brain. We examined the role of GalR1 in seizures by studying the susceptibility of GalR1 knockout (KO) mice to status epilepticus (SE) and accompanying neuronal injury.

SE was induced in GalR1 KO and wild-type (WT) mice by Li-pilocarpine, 60-minute electrical perforant path stimulation (PPS), or systemic kainic acid (KA). Seizures were analyzed with Harmonie software. Cell injury was examined with FluoroJade B- and terminal deoxynucleotidyl transferase–mediated uridine triphosphate nick end labeling; neurogenesis was studied by using bromodeoxyuridine labeling.

Compared with WT littermates, GalR1 KO showed more severe seizures, more profound injury to the CA1 pyramidal cell layer, as well as injury to hilar interneurons and dentate granule cells on Li-pilocarpine administration. PPS led to more severe seizures in KO as compared with WT mice. No difference in the extent of neuronal degeneration was observed between the mice of two genotypes in CA1 pyramidal cell layer; however, in contrast to WT, GalR1 KO developed mild injury to hilar interneurons on the side of PPS. KA-induced seizures did not differ between GalR1 KO and WT animals and led to no injury to the hippocampus in either experimental group.

No differences were found between KO and WT mice in both basal and seizure-induced neuronal progenitor proliferation in all seizure types. Li-pilocarpine led to more extensive glia proliferation in GalR1 KO than in WT, and in both mouse types in two other SE models.

In conclusion, GalR1 mediated galanin protection from seizures and seizure-induced hippocampal injury in Li-pilocarpine and PPS models of limbic SE, but not under conditions of KA-induced seizures. The results justify the development and use of GalR1 agonists in the treatment of certain forms of epilepsy.

Galanin Type 2 Receptors Regulate Neuronal Survival, Susceptibility to Seizures, and Seizure-induced Neurogenesis in the Dentate Gyrus

Mazarati A, Lu X, Kilk K, Langel U, Wasterlain C, Bartfai T

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The neuropeptide galanin has been implicated in inhibiting seizures and protecting hippocampal neurons from excitotoxic injury. In the hippocampus, galanin acts through two receptor subtypes, GalR1, expressed in CA1, and GalR2, abundant in dentate gyrus. We developed an approach to induce and to study selective semichronic knockdown of GalR2 in the rat hippocampus. A 50% reduction of GalR2 binding was achieved by continuous infusion of complementary peptide nucleic acid antisense oligonucleotide into the dentate gyrus. This resulted in an increase in the severity of self-sustaining status epilepticus induced by electrical stimulation of the perforant path, induced mild neuronal injury in the dentate hilus, augmented seizure-induced hilar injury, and inhibited seizure-induced neurogenesis in the subgranular zone of the dentate gyrus. Our data suggest that in the dentate gyrus, galanin, acting through GalR2, inhibits seizures, promotes viability of hilar interneurons, and stimulates seizure-induced neurogenesis. These results are important for understanding the role of galanin and galanin-receptor subtypes in the hippocampus both under normal conditions and in excitotoxic injury.

COMMENTARY

The two articles highlighted in this commentary are the latest of an elegant body of work by Mazarati and associates to demonstrate the anticonvulsant and neuroprotective properties of the neuropeptide, galanin. The anticonvulsant activity of galanin was demonstrated by Mazarati et al. (1) more than a decade ago in the picrotoxin-kindled seizure model. The recent articles highlighted here addressed the role of GalR1 and GalR2 receptors in mediating the effects of galanin on seizures, seizure-induced injury, and neurogenesis, and thus perhaps, epileptogenesis. Hippocampal GalR1 is found predominantly in the pyramidal cells of CA1 and to some extent of CA3, whereas GalR2 is present in the dentate granule cells. The role of GalR1 has been studied by using mice deficient in the GalR1 receptor in three seizure models: systemic lithium-pilocarpine–induced status epilepticus; kainic acid–induced status epilepticus; and self-sustaining status epilepticus, induced by focal stimulation of the perforant path. The role of GalR2 has been studied by effecting a 50% reduction in GalR2 by continuous infusion of complementary peptide nucleic acid (PNA), antisense oligonucleotide, into the dentate gyrus. Antisense PNA is similar to the standard antisense oligonucleotide but is linked by peptide bonds, which makes it resistant to hydrolysis.

The findings indicate that the absence of GalR1 produced more severe seizures in the animals treated with lithium-pilocarpine and perforant path stimulation (PPS), and that the former treatment produced more severe injury in the CA1 pyramidal cells. Kainic acid–induced seizures in the GalR1 knockout animals were similar, and neuronal injury was not seen in either the knockout or the wild-type animals. This lack of seizure-induced injury may be due to the known resistance to kainic acid–induced damage in the genetic background (C57Bl6) from which the knockouts derived. These results are consistent with the previous observation by Mazarati et al. (2) that galanin-overexpressing mice are resistant to seizure induction and, with the findings of Saar et al. (3), that a nonpeptide agonist of galanin functioned as an anticonvulsant, with its effects being abolished by the pretreatment of these rats with an antisense PNA targeted to GalR1. Thus a number of convergent studies confirm the anticonvulsant potential in targeting GalR1. The role played by GalR2 receptors also seems to be to inhibit seizures, as evidenced by increased severity of seizures when GalR2 is downregulated by antisense PNA. Further, reduction in GalR2 activation enhanced dentate hilar injury and inhibited seizure-induced neurogenesis. It would seem then that agonists of both GalR1 and GalR2, and even better perhaps, agonists that do not distinguish the receptor subtypes, would hold tantalizing therapeutic promise.

The promise of such an approach is nuanced because many classic anticonvulsants are known to have a pharmacologic propensity to antagonize seizures as well as to demonstrate behavioral sequelae and impair cognition (4). Indeed, galanin has been shown to have inhibitory actions on a variety of memory tasks, including the Morris water maze, delayed nonmatching to position test, T-maze delayed alternation, starburst maze, passive avoidance, active avoidance, and spontaneous alternation (5). However, it appears that GalR1-null mutants exhibit normal performance in a number of cognitive tasks (except trace version of cued fear conditioning) (6). In contrast, activation of GalR2 receptors by region-specific infusion of galanin to the dentate gyrus significantly retarded spatial acquisition without affecting swim speed or performance in the visible platform test in the Morris swim maze (7). These data suggest that perhaps an agonist targeting GalR1 is likely to be better tolerated.

Yet to be determined are the age-specific aspects of this pharmacology. Evidence has been presented that mice carrying loss-of-function mutation for the galanin gene actually grow up to be deficient in cholinergic neurons and show age-specific impairments in long-term potentiation and cognitive tasks (8). In addition to the suggested trophic role of galanin during development (8), a line of research suggests that galanin plasticity is a neuroprotectant, at least in models of Alzheimer disease (9). Another aspect of pharmacology yet to be worked out is whether the mode of administration (i.e., bolus vs. continuous) of galanin agonists may have paradoxically distinct effects on neuronal excitability and epileptogenesis [as was recently shown for brain-derived growth factor (10)] and what the implications of these distinct effects would be for therapy. The present state of unsatisfactory results in up to one third of patients with epilepsy who are being treated with the currently available anticonvulsant agents makes the future role of peptides, such as galanin, tantalizing and the emerging literature deserving of our attention.

by Raman Sankar, M.D., Ph.D.

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