AGING MODELS OF ACUTE SEIZURES AND EPILEPSY

Kevin M. Kelly, MD, PhD

Professor of Neurology, Neurobiology and Anatomy, Drexel University College of Medicine, Director, Center for Neuroscience Research, Allegheny-Singer Research Institute, Allegheny General Hospital, Pittsburgh

Aged animals have been used by researchers to better understand the differences between the young and the aged brain and how these differences may provide insight into the mechanisms of acute seizures and epilepsy in the elderly. To date, there have been relatively few studies dedicated to the modeling of acute seizures and epilepsy in aged, healthy animals. Inherent challenges to this area of research include the costs associated with the purchase and maintenance of older animals and, at times, the unexpected and potentially confounding comorbidities associated with aging. However, recent studies using a variety of in vivo and in vitro models of acute seizures and epilepsy in mice and rats have built upon early investigations in the field, all of which has provided an expanded vision of seizure generation and epileptogenesis in the aged brain. Results of these studies could potentially translate to new and tailored interventional approaches that limit or prevent the development of epilepsy in the elderly.

Models of Acute Seizures in Aged Mice

In aged animals, the most commonly used models employ electrical stimulation or a convulsant agent, such as kainic acid, pilocarpine, or pentylenetetrazol, to induce acute seizures. Depending on the model and the animal strain used, the results of studies of acute seizures in aged animals have variably demonstrated increased or decreased seizure susceptibility associated with advanced age. Early studies, using the BDF1 mouse strain (a cross between female C57BL/6 and male DBA/2 mice), explored the effect of aging on acute seizure susceptibility and demonstrated that the threshold for the tonic extensor component of maximal electroshock seizures increased with age (up to 30 months) (1). Similarly, the minimal effective concentration of pentylenetetrazol needed to induce maximal seizure activity increased in 24-month-old compared to 6-month-old animals (2), as did the sensitivity to the anticonvulsant effects of oxazepam (3) and phenobarbital in the same model (4). These studies suggested that aged BDF1 mice required increased levels of electrical or chemical stimulation to generate acute seizures, whereas decreased concentrations of anticonvulsants active at the $GABA_A$ receptor were required to mitigate pentylenetetrazol-induced maximal seizure activity.

Except for early studies of BDF1 mice, which showed equivalent effects in both male and female animals (1–3), relatively few studies have assessed gender-based differences in seizure susceptibility and/or neurodegeneration in mice. A study of seizure susceptibility in adult and aged animals of the inbred CBA strain demonstrated that 3-month-old males were distinctly more prone to seizures induced by the $GABA_A$ receptor antagonists, bicuculline and picrotoxin, compared to age-matched females; picrotoxin-induced seizure latencies were also decreased in the male animal (5). However, there was no gender-based difference in sensitivity to picrotoxin in 24-month-old animals. Comparing adult and aged male and female C57BL/6J mice following kainic acid treatment, aged female mice demonstrated more severe seizure activity, prominent hippocampal injury, and increased astrocyte proliferation (6). In studies not based on gender but using the same C57BL/6J strain, acute seizures were induced by a single electroconvulsive shock, followed by assessment of c-fos expression in different brain regions of varying age groups. All ages exhibited a transient increase in c-fos immunoreactivity, but in aged animals, the response was significantly less robust (7). Following a single dose of kainic acid, aged C57BL/6J mice were more sensitive to its pathological effects compared to adult animals, especially with regard to neuroinflammatory changes, as measured by markers of reactive gliosis (8). Comparing young adult, mid-aged, and aged C57BL/6J mice to similarly aged animals of the FVB/NJ strain, aged FVB/NJ mice were most vulnerable to kainic acid-induced seizure induction and associated neuropathological changes, which underscores the observations in other studies of aged mice—seizure-induced injury is regulated in a strain-dependent manner (9).

Although the senescence-accelerated mouse (SAM) has been widely used in geriatric research, its use for epilepsy has been limited. Using the SAM senile-prone (SAM-P8) strain,

Address correspondence to Kevin M. Kelly, MD, PhD, Professor of Neurology, Neurobiology and Anatomy, Drexel University College of Medicine, Director, Center for Neuroscience Research, Allegheny-Singer Research Institute, Allegheny General Hospital – 940 South Tower, 320 E. North Avenue, Pittsburgh, PA 15212-4772. E-mail: kelly@wpahs.org

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repeated kainic acid treatment resulted in these mice being more apt to have seizures and oxidative damage than age-matched, senescence-resistant mice and showed mitochondrial oxidative stress contributed to hippocampal degeneration (10,11). In a metallothionein-III (MT-III) knockout model, mice were more susceptible to seizures in old age. MT-III is a zinc-binding protein that is abundant in the synapses of glutamatergic neurons that release zinc and can modify neurotransmitter effects. Knockout animals have reduced zinc levels in several brain regions, including the hippocampus and cortex. The aged knockout mice were slightly more susceptible to severe kainic acid-induced seizures than wild-type controls but were significantly more prone to injury of CA3 cells following seizure activity (12).

These studies indicate that the expression of acute seizures in aged mice is variable, based on the strain and stimulation technique involved, but less so on the animal's gender. In general, compared to younger ages, aged animals were more susceptible to induced seizures, which were typically more severe and caused a greater degree of hippocampal degeneration. Although limited information suggests that aged animals may be more sensitive than younger animals to anticonvulsants active at GABAergic synapses, it is important to note that, historically, investigational antiepileptic drugs have not been tested in aged animals.

Models of Epilepsy in Aged Mice

Surprisingly, there have been relatively few studies that have focused on the development of epilepsy in aged mice. Following pentylenetetrazol kindling of 2- and 8-month-old SAMP8 mice, generalized convulsive seizures were seen for both ages over a period of 40 days, while atypical absence seizures were observed only in the 8-month group, which was more sensitive to the effects of phenobarbital and demonstrated higher concentrations of brain GABA glutamine, and glutathione compared to the younger group (13). Using the same model to assess glial–neuronal metabolic interactions, results from nuclear MRS and the administration of [1–^{13}C]glucose and [1,2–^{13}C]acetate revealed decreased labeling of [1–^{13}C]glucose in 8-month-old animals compared to controls, whereas 2-month-old animals had decreased labeling in glutamine from both the [1–^{13}C]glucose and [1,2–^{13}C]acetate (14). These results suggest the possibility that pentylenetetrazol kindling affected astrocytes in younger and glutamatergic neurons in older animals. In the presence of phenobarbital, the younger mice exhibited decreased labeling of most metabolites in all cell types from both labeled precursors, except in GABAergic neurons. Conversely, only GABAergic neurons were affected by phenobarbital, as indicated by increased GABA labeling (14). In a different study that assessed age-related differences in mRNA expression of $GABA_B$ receptors and mutated voltage-gated calcium channel $\beta 4$ subunits in the Cacnb4^{lh} (lethargic) model of absence seizures, 6-month-old animals demonstrated no change in $GABA_B$ receptor or Cacnb4^{lh} RNA expression compared to age-matched controls; in contrast, 2-month-old animals showed a significant correlation between the magnitude of increased $GABA_B$ receptor and decreased Cacnb4^{lh} RNA expression (15). It is difficult to extract common themes of an age-related expression of epilepsy from these few studies, which utilize different models of diverse epilepsies; however, distinct age-related differences were observed and suggest that these models can be used more fully to explore mechanisms of epileptogenesis and epilepsy in the aged brain.

Models of Acute Seizures in Aged Rats

Numerous studies have used rats of various postmature ages to study the effects of acute seizures in the aged brain. Low doses of kainic acid which were nontoxic in young Sprague–Dawley rats (5–6 months), caused status epilepticus, neuronal damage, and death in older animals (22–25 months), whereas mid-aged animals displayed intermediate effects (16). Expanding on these results, aged female Long–Evans rats (30 months) were shown to exhibit a higher rate of tonic–clonic seizures at lower doses of kainic acid than young adult animals (6 months), and kainic acid treatment caused a significant increase in the release of aspartate, glutamate, and norepinephrine in both aged Fischer 344 (F344) and Long–Evans rats, which was not observed in the adult animals (17). In addition to increased sensitivity to the convulsant effects of kainic acid, aged animals had altered responses to kainic acid-induced status epilepticus. The EEG responses in aged F344 rats (22–25 months) showed a reduction in some of the faster frequencies (12.5–35 Hz) as well as a higher frequency of preseizure events and shorter latency to Racine scale class 5 seizures, compared to younger animals (7–8 months) (18). Following 4-hour long, kainic acid-induced status epilepticus and animal sacrifice, brains of aged F344 animals (25–29 months) showed prominently decreased hippocampal expression of α_{1A}, α_{1C}, and α_{1D} subunits of voltage-gated calcium channels compared to younger animals (5–14 months) (19). Kainate-induced status epilepticus in young adult and aged F344 rats was not associated with enhanced hippocampal neurogenesis in the aged animals (20). In a recent study using young adult and aged Sprague–Dawley rats, kainic acid injection resulted in increased seizure susceptibility, oxidative stress, and hippocampal pyramidal cell loss in the aged animals only (21).

A series of studies, which used kainic acid to induce focal hippocampal injury, but not acute seizures, in young adult, mid-aged, and aged F344 rats, demonstrated that aged animals had the greatest reduction of dentate hilar neurons (22) but

no significant change in GAD-67+ interneuron populations in any of the hippocampal layers and subfields (23). In addition, the aged brain contained decreased amounts of brain-derived neurotrophic factor compared to younger animals, suggesting potentially diminished synaptic reorganization and dentate neurogenesis after injury (24). Finally, grafting of CA3 cells, enriched with fibroblast growth factor 2, into aged hippocampus showed increased neuronal integration compared to mid-aged animals (25); whereas, grafting embryonic neural stem cells into aged hippocampus did not exhibit migration into injured areas or widespread neuronal differentiation (26), and the ability of these cells to enhance neurogenesis was lost by mid-age (27). The broad range of studies utilizing kainic acid and aged rats to investigate the effects of acute seizures and status epilepticus, or to induce focal hippocampal injury, point to the relative simplicity and versatility of this approach to study a variety of aging-related phenomena.

Studies evaluating the effects of age on acute seizures in rats have used chemicals other than kainic acid. For instance, the common convulsant pilocarpine demonstrated a lowered seizure threshold in aged, 24-month-old Wistar rats (28). Aged F344 rats (24 months) had an increased sensitivity to strychnine-induced seizures and higher mortality rates, which corresponded to a reduction in [^{3}H]strychnine and [^{3}H]GABA binding in the medulla and spinal cord (29). In contrast to the effects of pilocarpine and strychnine, nicotine-induced convulsions were delayed and abbreviated in 24-month-old Wistar rats when compared to younger animals, despite the half-life of nicotine being longer in the older animals (30). The decreased seizure response possibly is related to a muted corticosterone release in response to the nicotine. In a similar vein, aminooxyacetic acid appeared to lose some potency over the lifespan of Wistar rats; most of the loss appeared to occur within the first 10 months (31). In a different study also using Wistar rats, cortical injection of $FeCl_3$ in 4- and 18-month-old animals resulted in faster seizure spread and a lower latency for generalization of electrobehavioral seizure activity in the older animals (32). The variability of effects in these studies suggests, at a minimum, a spectrum of potency and efficacy for the generation of acute seizures by the convulsant agent, which is in part related to differences in each agent's metabolism in aged animals.

Using electrical stimulation to induce acute seizures, there was no observed effect of age on the seizure threshold with direct cortical stimulation in BN/BiRij rats. Very old animals (35 months) were more sensitive to the anticonvulsant effect of oxazepam and did not display the proconvulsant effects at higher doses that were seen in younger animals (33). In another study, using Wistar rats, increased blood–brain barrier permeability to macromolecules was seen in 24-month-old animals after 10 electroconvulsive shocks (but not after one), suggesting that the older animals are more susceptible to injury caused by repeated seizures (34).

Several studies in Sprague–Dawley rats have investigated the effects of age on the brain's transcriptional response to acute pentylenetetrazol-induced seizures. The original work focused on the immediate early gene, c-fos, which has been associated with brain plasticity. Young animals that were given a convulsive dose of pentylenetetrazol (50 mg/kg) transiently upregulated c-fos mRNA. Among aged animals (30 months), this response was delayed (i.e., a longer time to an observed increase) and blunted (i.e., a smaller maximum upregulation), although the basic response remained intact (35). Using the same stimulus, a similar pattern in the cortex and hippocampus was observed with tissue plasminogen activator (tPA) mRNA. Interestingly, the cortical transcriptional response, while present in all layers in the young animals, was limited to layer V neurons in the older (18 month) animals (36). In contrast, transient increases in microtubule-associated protein 1B (MAP1B), which is also associated with brain plasticity, occurred at earlier times in older animals (although the responses were significantly reduced) compared to their young counterparts (37). The most recent work in this model showed that old animals lose the ability to regulate axonal growth-associated protein 43 (GAP-43) in certain brain areas (38). These results demonstrate a general reduction of transcriptional responses for several proteins following induced seizures in aged brain and may be directly related to the limited plasticity and functional recovery often observed in injured aged brain tissue.

In addition to in vivo models of acute seizures, *in vitro* models have been developed using brain tissue from aged animals. Epileptiform activity was induced by withdrawing Mg^{2+} from the media hippocampal–entorhinal cortex slice preparations from Wistar rats; compared to adults (12–14 weeks), slices from aged animals (24–26 months) had reduced seizure spread and conduction velocity, as assessed by optical imaging (39). This observation was confirmed in a similar study using 4-aminopyridine as the convulsive agent: propagation velocities were shown to be slower and the location of seizure onset became more focused in the neocortex of aged animals compared to adults (40). Using hippocampal slices from adult and aged F344 rats, stimulation of the molecular layer evoked population spikes from aged but not adult slices. Similarly, recordings from the CA3 field demonstrated multiple spikes from aged, but not adult slices, which frequently evolved into spontaneous epileptiform bursts, suggesting an increased susceptibility of aged hippocampus to seizure generation (41).

Models of Epilepsy in Aged Rats

Some of the earliest work in the geriatric epilepsy field was done in F344 rats using kindling by electrical stimulation. It

was shown that the hippocampal kindling speed of aged animals (26 months) was markedly delayed and correlated with decreased performance on a memory task (42). In addition, kindling speed with pentylenetetrazol was delayed in aged Wistar rats as well. Administering a subconvulsive dose every 48 hours resulted in fully kindled animals when they were 6 months of age or younger; 18- and 24-month-old animals never developed generalized clonic or tonic–clonic convulsions (43). In addition to the use of kindling studies to model epilepsy in aged rats, genetically epileptic animals have been a valuable resource to model epileptic seizures induced by environmental stimuli. Genetically, epilepsy-prone rats (GEPRs) are predisposed to audiogenic seizures and have a lower threshold for electroshock and pentylenetetrazol-induced seizures than other strains. There are two distinct GEPR colonies: GEPR-9 (severe seizures) and GEPR-3 (moderate seizures). Using juveniles (<65 days), seizure severity increased and latency decreased in GEPR-9s with increasing age, but no significant differences were seen in these parameters between the young adults and senescent animals (480–540 days) (44).

In another genetically determined form of epilepsy, the spontaneous spike-wave discharges of older Wistar rats have been used to model absence epilepsy in the elderly. It has been shown that both the number of spike-wave discharges and of animals with absences increased with age (45). In another study, the L-type calcium channel agonist Bay K 8644 significantly reduced the number of these discharges (46). More recently, it was shown that CGP 35348, a $GABA_B$ antagonist, strongly suppressed the number and duration of spike-wave discharges (47). Using aged F344 rats, which also demonstrate spontaneous spike-wave discharges, administration of CGP 35348 alone or in combination with other AEDs reduced spontaneous spike-wave discharges as well as spike-wave discharges enhanced by the addition of the convulsant trimethylolpropane phosphate (48). The results of these studies using Bay K 8644 and CGP 35348 indicate the importance of voltage-gate calcium channels and $GABA_B$ receptors in the regulation of spontaneous spike-wave discharges, as demonstrated in the mouse (15). In a different study, using a nonlinear measure of brain dynamics to compare the immediate preictal and postictal periods of spike-wave discharges in 4- and 20-month F344 rats, outcomes suggested that age-related changes in spike-wave discharges might be associated with resetting mechanisms of brain dynamics (49). Although spike-wave discharges were observed in 2- to 30-month-old F344 rats, in a model of poststroke epilepsy generated by cortical photothrombosis, mid-aged and aged animals also developed Racine class 3 convulsive seizures that appeared to originate in the peri-infarct region (50). The results from both kindling and genetically based studies of epileptic seizures suggest potentially ideal methodological approaches for the further study of epilepsy in aged rats.

Conclusions

The work described in this review provides a foundation for future exploration and development of animal models of geriatric epilepsy. As the population continues to live longer and healthier lives, researchers will need to advance the understanding of geriatric epilepsy in order to expand and improve available treatment options for this patient population.

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