Introduction

The prevalence and incidence of epilepsy increase significantly in the elderly (people older than 60 years). In addition, the aging population has a significantly higher chance of developing status epilepticus. These, and other related factors, may be expressed in two ways: (1) The expression of existing seizures and epilepsy (both inherited and acquired) may change as a function of the changes associated with aging; and (2) Seizures and epilepsy may occur de novo, sometimes as a result of conditions associated with aging such as stroke, brain trauma, tumors, and neurodegenerative disorders. Since aging is not a condition of the CNS alone, aging-associated changes in other organ systems (such as in liver metabolic capacity and renal clearance) may have important effects on the way a patient’s antiepileptic medication is metabolized or cleared, thus affecting seizure expression.

The population of elderly persons worldwide, especially in developed countries, is increasing at a high rate. Trends predict that by 2050, the population over 60 years of age will comprise more than 30% in many countries. This increase calls for new and innovative diagnostic and treatment options for elderly patients with epilepsy. Increased needs in patient care should also be reflected in enhanced research in this area. Yet, there remains an alarming gap between the increasing numbers of elderly people with either new or modified seizures and basic research in the field. A recent study suggested that between 1965 and 2003, there were only 30 scientific articles investigating the condition of seizures in the aging brain. From 2003 through 2006, a few additional studies pushed up the number of papers up to about 50. Finally, in 2007, a volume of International Review of Neurobiology appeared that was devoted to this topic. Even with this modest surge in research, a critical mass of knowledge of basic mechanisms leading to significant improvements in seizure diagnosis and treatment in elderly patients has not been achieved. The need is pressing.

Seizures in the elderly are further confounded by the fact that age cannot be simply used as a covariant or grouping variable. Physical conditions of elderly people may be very different even within the same age group. A 60-year-old person with poor health and physical condition may be at a higher risk of seizures than an 80-year-old person in excellent health. Thus, it seems that, as in the case of the early postnatal development, aging studies need to be carried out in several distinct age groups of experimental animals to fully appreciate different conditions associated with aging in humans with seizures. Models of seizures in aged animals should also include some of the underlying conditions frequently occurring in the elderly. That is, the models should include stroke or brain injury within the context of an aging brain, to better mimic the human situation.

Background

Studies on animal models performed so far have investigated, both in vivo and in vitro, mechanisms of seizures and epilepsy in aged rats with normal as well as impaired brain. Unfortunately, some of these studies have sometimes generated inconsistent findings.

To make studies on rodent models relevant to human aging, it is important to define ‘aged’ in rats. With a life expectancy between 750–850 days, rats beyond 600 days of age can be considered aged. In studies using the kainic acid model to induce seizures in adult and aged rats, there were no differences in peak severity of status epilepticus. However, the progression through seizure stages was different; aged rats reached each seizure stage earlier than adult rats, suggesting an increased susceptibility in the aged brain. In contrast, in the hippocampal kindling model, aged rats kindled more slowly (i.e., required more kindling stimulations to reach the criterion of five generalized stage 5 seizures) than adult rats. Despite this slower kindling rate, aged rats displayed longer after-discharges and faster propagation of epileptiform activity to the contralateral hemisphere.

An in vitro model focused on the features of the hippocampal circuitry to account for age-related differences in susceptibility to kainic acid (KA)-induced seizures. In hippocampal slices, the frequency of inhibitory postsynaptic potentials in granule cells is significantly decreased in aged rats than in adult rats. Further, perforant path stimulation at 5 Hz for 10 s produces multiple population spikes in granule cells as a response to a single stimulus in about 40% of aged rats but in none of adult rats, indicating an impairment of dentate gyrus filtering as a function of age.
Some studies focused on the effects of stroke (using the 
model of middle cerebral artery occlusion: MCAO) on the 
development of seizures with aging. One year after 
after MCAO, there was no evidence of behavioral or EEG 
seizure activity in the region of the occlusion. More 
recent studies have employed photothrombotic brain ves-
ticle occlusion, with Rose Bengal stain and transcranial 
ilumination of a relatively restricted area of the neocor-
tex. Spontaneous seizures in rats subjected to this injury 
developed only in few cases (7/36) over a period of 
10 months after the insult. However, other studies 
have reported that 35–100% animals exhibit seizures 
4–10 months after cortical photothrombosis, with seizures 
occurring up to several times per day.

An in vitro model system of stroke-induced epilepsy 
used glutamate-induced injury in hippocampal neuronal 
cultures. Neurons that survived yet incurred damage 
(a correlate of penumbra neurons in stroke) developed 
epileptiform discharges and network oscillations that per-
sisted throughout their life in culture. This model has 
potential for studying the mechanisms associated with 
stroke-induced epilepsy, since the culture model is easily 
accessible for electrophysiologic, biochemical, and imag-
ing studies.

Methodology

Both mice and rats are used in seizure models. Mice 
are more commonly used to study genetic modifications 
that alter seizure susceptibility, while rats are more 
appropriate for acute seizure models. However, none of 
the models described in the following sections have been 
explored and utilized systematically in aged animals.

Mice

One of the convenient mouse models for studies of 
seizures and epilepsy in aging may be the senescence-
accelerated mouse (SAMP8). This mouse is often used 
in geriatric research, and information gleaned from such 
studies might aid investigations of epilepsy during aging. 
Another mouse strain potentially useful for aging studies 
is the metalllothionein-III (zinc-binding protein) knock- 
out mouse. Of course, aged common mouse strains (such 
as BDF1 mice and C57BL/6J) should also be investigated 
in epilepsy research.

Rats

Aged (i.e., >600 days old) Sprague-Dawley, Long-Evans, 
and Fisher 344 rats are more sensitive to KA-induced 
seizures than adult rats. These findings are consistent 
with the human condition of increased seizure suscepti-

bility with aging. Other convulsants, such as pentylenetet-
razole and strychnine, have also been used to study 
seizure susceptibility in aged rats, and invariably indicate 
that aged rats develop seizures at lower thresholds than 
younger adult animals.

KA-Induced Seizures

Seizures are elicited usually using systemic injection of 
aqueous solution of KA (with pH adjustment), a neuro-
toxic analog of glutamate with preferential effects on the 
limbic system. To elicit clonic seizures without loss of 
righing (sometimes termed ‘limbic seizures’) that evolve 
into status epilepticus, a bolus dose of KA is administered 
intraperitoneally. In adult rats, the effective dose is 
between 10–20 mg kg$^{-1}$, while mice usually require a 
higher dose (between 20–40 mg kg$^{-1}$). An alternative 
approach is to infuse graded doses of KA into the tail 
vein, usually 2.5–5 mg kg$^{-1}$ in rats every 5–20 min until 
seizures occur.

Pentylenetetrazole (PTZ)-Induced Seizures

Seizures are elicited most commonly by a bolus dose of 
subcutaneous aqueous solution of 50–100 mg kg$^{-1}$ in both 
rats and mice. This dose results in blockade of the GABA$\text{A}$ 
receptor via the TBPS ($\beta$-butyrbicyclophosphorothionate) 
site in the chloride channel. If the dose used is at the lower 
end of the range, PTZ induces bilateral clonic (myo-
clonic) seizures of face and forelimbs without loss of 
righing. With higher doses, these seizures progress to
tonic-clonic seizures of all four limbs with loss of righting. As in the case with KA, graded PTZ doses can be delivered intravenously, allowing the determination of seizure threshold.

Strychnine-Induced Seizures

Seizures are elicited by injection of strychnine solution (aqueous; 1 mg ml\(^{-1}\)), usually intraperitoneally, at a dose range of 1–4 mg kg\(^{-1}\) in both rats and mice. Strychnine induces tonic-clonic convulsions with loss of righting and prominent hyperextension, including the tail (‘Straub-tail’).

Kindling

Kindling is a process by which subconvulsant electrical stimuli, delivered at intervals (usually daily) to various brain structures (e.g., olfactory bulb, amygdala, perforant path), eventually cause local seizure activity (after-discharge) that can progress to limbic seizures and finally to generalized seizures. The classic protocol for kindling uses electrical stimuli at 50–60 Hz for 1–2 s delivered via electrodes in the amygdala or hippocampus, with 24-h interstimulus intervals. The stimulation that evokes a kindled seizure will cause seizures even weeks or months later.

Results

Data from experiments performed on aged animals provide information about the seizure propensity of the aged brain. Studies carried out so far have been consistent with observations made on the human population, attesting to the increased incidence and prevalence of seizures and epilepsy as a function of age. These studies will also provide information about the conditions leading to these age-related changes in seizure susceptibility.

Mice

The SAMP8 mouse displays increased susceptibility to KA seizure-induced damage compared with the animals of the same age without the ‘aging mutation,’ but few studies have used this model to study seizures and epilepsy in aging. Similarly, aged metallothionein-III knock-out mice are more susceptible to KA seizure-induced damage than the wild-type age-matched controls. Finally, within common mouse strains (BDF1 and C57BL/6J), aged animals display increased susceptibility to PTZ- and KA-induced seizures.

Rats

In aged Long-Evans rats, administration of KA elicits increased release of aspartate, glutamate, and norepinephrine compared to adult controls. This enhanced neurotransmitter release in response to KA might underlie the increased seizure susceptibility seen in aged subjects (compared adult control rats). Other differences seen in the aged rats’ response to KA include a delayed c-fos expression and altered regulation of microtubule-associated protein and axonal-growth associated protein. However, more research is necessary to determine whether these changes are a consequence of seizures themselves. Future studies should concentrate not simply on whether the aged brain is more susceptible to seizures (we already know this to be the case), but why the aged brain is more seizure susceptible. Such information might improve treatment options for elderly patients.

Future Goals

Several goals should be addressed promptly in research on aging and epilepsy. First, we need to collect significantly more descriptive information about seizures in aged animals, to correlate with human data. Second, experiments need to move beyond description into mechanism. Only at that point will we be able to identify potential therapeutic interventions that might target age-related modifications of brain structure and function. In that regard, the efficacy of antiepileptic drugs needs to be studied in parallel with the earlier-mentioned experiments, always keeping in mind the need for appropriate adult controls.

There are some big challenges to achieving these goals. Research on aged animals is expensive because of the steep costs of purchasing aged animals or maintaining adult rats into senescence. The distinction between causation and association must be considered carefully in experiments on epileptogenesis during aging. Investigators must keep in mind the difference between reactive seizures (possibly with lower seizure threshold as a function of various age-related neural changes) versus the development of the epileptic state. Data must be interpreted in the context of ongoing age-related brain changes as well as aging in other organ systems. For example, is it possible that the higher susceptibility to KA-seizures in aged rats partially reflects age-related liver metabolic changes?

Despite those challenges, there is an enormous opportunity to explore and define age-related changes in seizure susceptibility and epileptogenesis, as this field has been ignored (with a few notable exceptions) in experimental laboratories. With the burgeoning population of elderly citizens, the need to understand and develop new treatment modalities is urgent.
Further Reading


Abstract:
By 2050, elderly people (older than 60 years) will exceed 30% of the total world population. It is now recognized that this population has a high incidence of seizures and epilepsy. Possible reasons include enhanced seizure predisposition, medical comorbidities, structural changes of the brain related to aging, and synergistic effects of concurrent medications. Underlying conditions in aging patients may modify the expression of seizures that have been chronically present in the younger individual, or the aged brain may develop seizures de novo. Metabolism of antiepileptic drugs may be also significantly different in the elderly, with drug interactions becoming a serious issue. The few models in aged animals (mice and rats) that have been investigated to date confirm an increased susceptibility of the aged brain to develop seizures. More research is needed on mechanisms of increased seizure propensity in elderly, and on anticonvulsant drug effects on the aging brain.

Keywords: Aging; Epilepsy; Fisher 344 rat; Life expectancy; Population; Seizure; Senescent mouse; Stroke; Trauma

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