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Strain and Age Affect Electroconvulsive Seizure Testing in Rats

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Summary

Electroconvulsive seizure thresholds were compared between adolescent and mature Sprague-Dawley, Wistar, and Fischer rats. All strains had similar hindbrain or forebrain seizure thresholds as adolescents. As adults, hindbrain or forebrain seizure thresholds were highest for Sprague-Dawley and lowest for Fischer rats. Conversely, limbic seizure thresholds during adolescence were highest for Fischer rats. Additional study is needed to better delineate strain and maturational effects on electroconvulsive seizure testing.

Keywords

maturation; development; epilepsy

Introduction

Rat strain and age alter outcome in kindling and chemoconvulsant seizure models (Loscher, et al., 1998; Racine, et al., 1973); however, strain or age effects on electroconvulsive seizure testing are not well defined. Mouse strain influences electroconvulsive seizure thresholds (Frankel, et al., 2001), but data in rats are lacking. We compared adolescent and adult electroconvulsive seizure thresholds for Sprague-Dawley, Wistar, and Fischer rats. Based on strain and age effects on amygdala kindling (Loscher, et al., 1998; Racine, et al., 1973) and chemoconvulsant sensitivity (Golden, et al., 1995), we hypothesized that electroconvulsive seizure thresholds would be lower for Sprague-Dawley vs. Wistar or Fischer rats, as well as increase with age in a strain-specific manner.

Methods

Male Sprague-Dawley, Wistar, and Fischer rats (n=30/strain) were purchased from Charles River Laboratories (Raleigh, NC), housed in a temperature- and light-controlled (12 h on/12 h off) environment, and allowed free access to food and water. The University of Utah Institutional Animal Control and Use Committee approved all animal care and experimental interventions.

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Three standard transcorneal electroconvulsive seizure paradigms were applied to determine hindbrain, forebrain, and limbic seizure thresholds (Barton, et al., 2001; Frankel, et al., 2001; Otto, et al., 2004). All testing was conducted January – February, 12pm – 6pm. Tetracaine (0.5%) in 0.9% saline was applied to the cornea just prior to stimulation. All strains were tested concurrently. Individual rats were tested only once per day. Testing for a single seizure type was completed on a single day. Testing for different seizure types was separated by at least 48 hours of rest (Freeman and Jarvis, 1981).

A previously described stimulator (Woodbury and Davenport, 1952) (frequency 60 Hz, 0.2 msec sinusoidal current pulse, and stepwise current intensity) was used for hindbrain and forebrain seizure testing. Hindbrain seizure thresholds were assessed by tonic hindlimb extension (THE) seizure activity on PND 34 and 60 (Browning and Nelson, 1985; Eells, et al., 2004). THE seizures begin as tonic forelimb extension, spread to hindlimb flexion, and terminate in full tonic hindlimb extension. Forebrain seizure thresholds were assessed by minimal clonic seizure activity on PND 37 and 63 (Browning and Nelson, 1985; Eells, et al., 2004). Minimal clonic seizures are manifest as rhythmic face and forelimb clonus, rearing and falling, and ventral neck flexion.

As described by Barton, et al. (2001), a Grass stimulator (Model S4B, frequency 6 Hz, stimulus duration 3 sec, 0.2 msec rectangular current pulse, and stepwise current intensity) was used for limbic seizure testing on PND 40. Limbic seizure thresholds were assessed by partial psychomotor seizure activity, which is characterized by rhythmic facial movements, forelimb clonus, dorsal neck flexion, rearing and falling, and transient ataxia (Barton, et al., 2001). Due to technical difficulty applying the necessary 3-sec transcorneal stimulus in larger rats, limbic seizure thresholds were assessed only during adolescence.

Population seizure thresholds were determined for each paradigm via the staircase estimation procedure (Finney, 1971). Full convulsive current (CC) curves were generated and compared using Probit analysis (Minitab, State College, PA). Rat weights were compared by multiple analysis of variance, with Tukey's test for post-hoc analysis (SPSS version 11.0 for MAC, Chicago, IL). Seizure thresholds were defined, *a priori*, as the CC at which 50% of rats exhibit seizures (CC_{50}). A p-value < 0.05 was considered significant.

Results

Size and weight differed between strains ($p < 0.05$). Respective mean (95% confidence interval) weights for Sprague-Dawley, Wistar, and Fischer rats were 120 (114-124) g, 151 (146-156) g, and 92 (89-95) g during adolescence and 362 (350-374) g, 359 (354-365) g, and 224 (221-227) g at maturity.

Thresholds were higher for THE than minimal clonic seizures ($p < 0.05$; Table 1), due to the higher current intensities needed to excite hindbrain vs. forebrain structures via transcorneal stimulation (Browning and Nelson, 1985). All strains had similar hindbrain or forebrain seizure thresholds as adolescents (Table 1). As adults, hindbrain seizure thresholds were highest for Sprague-Dawley, intermediate for Wistar, and lowest for Fischer rats ($p < 0.05$). Similarly, forebrain seizure thresholds were higher for either Sprague-Dawley or Wistar vs. Fischer adult rats ($p < 0.05$). Hindbrain and forebrain seizure thresholds increased with age for all strains ($p < 0.05$); however, the magnitude of change was strain-specific (Table 1). Sprague-Dawley rats showed the most maturational change, and Fischer rats showed the least. Limbic seizure thresholds, determined during adolescence, were highest for Fischer rats ($p < 0.05$, Table 1). In addition, Sprague-Dawley rats had a trend toward higher limbic seizure thresholds than Wistar rats ($p = 0.083$).

Discussion

Amygdala kindling acquisition is faster for Sprague-Dawley than Wistar or Fischer rats (Loscher, et al., 1998; Racine, et al., 1973). Consequently, we anticipated that electroconvulsive seizure thresholds would be lowest for Sprague-Dawley rats. As predicted, partial psychomotor seizure thresholds during adolescence were lower for Sprague-Dawley than Fischer rats. This may be explained, in part, by limbic system involvement in both amygdala kindling and partial psychomotor seizures. It is unclear why limbic seizure thresholds were different between strains during adolescence, yet hindbrain and forebrain thresholds were not. Notably, Wistar rats, which unexpectedly showed the lowest limbic seizure thresholds, do have a propensity to develop spike-wave seizures (Vergnes, et al., 1987). The contribution of this predisposition to our findings is unclear and beyond the scope of this initial report.

In contrast to psychomotor seizure thresholds, hindbrain and forebrain seizure thresholds were higher for adult Sprague-Dawley rats. Further, thresholds increased with age for all strains, but the degree of change was strain-specific. Strain also affects maturational changes in amygdala kindling and chemoconvulsant sensitivity. Kindling acquisition rates are faster for younger Sprague-Dawley rats (Moshe, 1981); however, this finding is not corroborated in hooded rats (Gilbert and Cain, 1981). Strain and age effects on kainic acid sensitivity closely mirror our observations. Thresholds for kainic-acid induced seizures are similar between adolescent Sprague-Dawley and Fischer rats but higher for adult Sprague-Dawley (vs. Fischer) rats (Golden, et al., 1995).

Our findings suggest that strain differentially affects regional neural network connectivity and excitability. In corroboration, hippocampal granule cells have strain-specific roles in amygdala kindling (Tsunoda, et al., 1995). Strain may likewise influence cerebral response to nervous system injury (Paulson, et al., 2005). Strain influences are largely unexplored in epilepsy models, yet may prove important, especially for study of acquired epilepsy, such as that induced by hypoxia-ischemia or traumatic brain injury.

To our knowledge, ours is the first report of rat strain and age effects on electroconvulsive seizure threshold testing. Additional investigation is indicated to better delineate strain and age effects on electroconvulsive seizure testing, as well as the study of epilepsy after a defined cerebral insult.

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Table 1

Strain-specific Seizure Thresholds

	CC_{50} (95% confidence intervals) in mA		Increase with Age
	Adolescence	**Maturity**	
THE			
Sprague-Dawley	31.3 (28.9 - 33.7) $^{\infty}$	53.3 (51.8 - 54.9) $^{*\,\hat{}}$	70%
Wistar	29.8 (29.5 - 32.2) $^{\infty}$	45.8 (44.2 - 47.4) $^{\hat{}}$	54%
Fischer	28.8 (26.3 - 31.1) $^{\infty}$	39.5 (37.8 - 41.2)	37%
Maximal Inter-strain Difference	8%	35%	
Clonic			
Sprague-Dawley	16.2 (15.4 - 17.1) $^{\infty}$	25.7 (24.4 - 26.7) $^{\hat{}}$	59%
Wistar	16.6 (15.9 - 17.5) $^{\infty}$	25.4 (24.0 - 26.7) $^{\hat{}}$	53%
Fischer	16.8 (16.0 - 17.6) $^{\infty}$	22.3 (21.0 - 23.6)	33%
Maximal Inter-strain Difference	3.7%	15%	
Psychomotor			
Sprague-Dawley	85.8 (82.1 - 90.3) $^{\hat{}\,\#}$		
Wistar	81.8 (78.1 - 84.8) $^{\hat{}}$		
Fischer	92.3 (89.1 - 96.3)		
Maximal Inter-strain Difference	13%		

$^{\infty}$ $p < 0.05$ vs. maturity for same strain;

* $p < 0.05$ vs. Wistar for same age and seizure type;

$^{\hat{}}$ $p < 0.05$ vs. Fischer for same age and seizure type;

$^{\#}$ $p < 0.1$ vs. Wistar for same age and seizure type