Neuroscience 288 (2015) 120–134

AGE-DEPENDENT LONG-TERM STRUCTURAL AND FUNCTIONAL EFFECTS OF EARLY-LIFE SEIZURES: EVIDENCE FOR A HIPPOCAMPAL CRITICAL PERIOD INFLUENCING PLASTICITY IN ADULTHOOD

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Abstract—Neural activity promotes circuit formation in developing systems and during critical periods permanently modifies circuit organization and functional properties. These observations suggest that excessive neural activity, as occurs during seizures, might influence developing neural circuitry with long-term outcomes that depend on age at the time of seizures. We systematically examined long-term structural and functional consequences of seizures induced in rats by kainic acid, pentylenetetrazol, and hyperthermia across postnatal ages from birth through postnatal day 90 in adulthood (P90). Magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and electrophysiological methods at ⩾P95 following seizures induced from P1 to P90 demonstrated consistent patterns of gross atrophy, microstructural abnormalities in the corpus callosum (CC) and hippocampus, and functional alterations in hippocampal circuitry at ⩾P95 that were independent of the method of seizure induction and varied systematically as a function of age at the time of seizures. Three distinct epochs were observed in which seizures resulted in distinct long-term structural and functional outcomes at ⩾P95. Seizures prior to P20 resulted in DTI abnormalities in CC and hippocampus in the absence of gross cerebral atrophy, and increased paired-pulse inhibition (PPI) in the dentate gyrus (DG) at ⩾P95. Seizures after P30 induced a different pattern of DTI abnormalities in the fimbria and hippocampus accompanied by gross cerebral atrophy with increases in lateral ventricular volume, as well as increased PPI in the DG at ⩾P95. In contrast, seizures between P20 and P30 did not result in cerebral atrophy or significant imaging abnormalities in the hippocampus or white matter, but irreversibly decreased PPI in the DG compared to normal adult controls. These age-specific long-term structural and functional outcomes identify P20–30 as a potential critical period in hippocampal development defined by distinctive long-term structural and functional properties in adult hippocampal circuitry, including loss of capacity for seizure-induced plasticity in adulthood that could influence epileptogenesis and other hippocampal-dependent behaviors and functional properties. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: epilepsy, hippocampus, dentate gyrus, *in vivo* imaging, developmental plasticity, critical periods.

INTRODUCTION

During postnatal brain development, electrical activity promotes synapse formation and organizes connectivity in immature circuits into networks supporting adult function and behaviors (Sur and Rubenstein, 2005). The developing brain also demonstrates age-specific susceptibility to seizure induction, presumably corresponding to age-specific differences in structure, physiology and metabolism influencing the synchronous electrical network activity that defines seizures (Moshe, 1993; Hauser, 1994; Swann et al., 1999; Sankar et al., 2002; Haut et al., 2004; Swann, 2005; Ben-Ari and Holmes, 2006; Holmes, 2009). These observations suggest that network synchronization during seizures in the developing brain may influence activity-dependent postnatal developmental processes such as formation and remodeling of neural connections and functional network properties (Crabtree et al., 1981; Ostrach et al., 1984; Swann et al., 1992, 1999; Bavelier and Neville, 2002; Pascual-Leone et al., 2005).

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Abbreviations: AD, afterdischarge; ANOVA, analysis of variance; CC, corpus callosum; $D_{||}$, axial diffusivity; $D_{\perp}$, radial diffusivity; DEC, directionally encoded color; DG, dentate gyrus; DTI, diffusion tensor imaging; FA, fractional anisotropy; HT, hyperthermia; ICV, intracerebroventricular; IM, intramuscular; IP, intraperitoneal; IPIs, interpulse intervals; KA, kainic acid; LV, lateral ventricle; LVV, lateral ventricular volume; MD, mean diffusion; ML, molecular layer; MRI, magnetic resonance imaging; pEPSPs, population excitatory postsynaptic potentials; PFA, paraformaldehyde; PPI, Paired-pulse inhibition; PS, population spike; PTZ, pentylenetetrazol; ROI, region of interest; SE, status epilepticus.

http://dx.doi.org/10.1016/j.neuroscience.2014.12.017
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Although specific details about age-dependent seizure susceptibility and the consequences of developmental seizures are debated, experimental evidence demonstrates that early-life seizures in rodents have distinctive effects which differ from seizures occurring during adulthood (Holmes and Ben-Ari, 1998; Lynch et al., 2000; Sankar et al., 2002; Ben-Ari and Holmes, 2006; Sankar and Rho, 2007). For example, seizure-induced cell loss and axonal reorganization are prominent consequences of recurring seizures in adulthood, but are much less evident after seizures occurring during early postnatal development (Holmes and Ben-Ari, 1998; Sankar et al., 2002; Haut et al., 2004; Ben-Ari and Holmes, 2006; Sankar and Rho, 2007). Seizures at specific time points during development induce abnormal network properties and structural differences at the cellular level (Cilio et al., 2003; Haut et al., 2004; Ben-Ari and Holmes, 2006; Holmes, 2009) and clinically relevant functional abnormalities including long-term diminished cognitive task performance (Lynch et al., 2000; Sayin et al., 2004; Karnam et al., 2009) suggesting that normal brain development is modified by seizures early in life.

Deprivation methods and modification of afferent activity in developing sensory and language systems provide substantial evidence of activity-dependent, age-specific developmental effects, including the existence of critical periods (Hubel and Wiesel, 1970; Hensch, 2004, 2005) in which deprivation of neural activity produces long-term structural and functional effects in cortical circuitry. The effects of deprivation or excessive neural activity during development are less clear in the hippocampus and limbic system. Induction of synchronous network events such as seizures during postnatal development provides an experimental opportunity to assess effects of excessive pathological electrical activity during development on adult hippocampal organization and function. Although it is known that the dentate gyrus (DG) undergoes substantial postnatal development (Schlessinger et al., 1975; Bayer, 1980), there have been few systematic comprehensive investigations into the effects of seizures induced across the broad range of ages from birth to adulthood on hippocampal development.

The purpose of this study was to systematically investigate the age-dependence of long-term consequences of seizures during postnatal development. Seizures were evoked across a range of ages (P1–90) using three models of induction: status epilepticus (SE) by kainic acid (KA), repeated self-limited seizures evoked by pentylenetetrazol (PTZ), and repeated seizures evoked by hyperthermia (HT). Structural effects and functional circuit properties were then examined in adulthood (> P95) using ex-vivo diffusion tensor imaging (DTI) and magnetic resonance imaging (MRI) to identify microstructural brain abnormalities, paired-pulse inhibition (PPI) as a measure of hippocampal network functional properties, and kindling to assess vulnerability to seizure-induced plasticity. The combination of these approaches demonstrated consistent age-dependent patterns of long-term structural and functional consequences of seizures during development, which varied systematically as a function of age at the time of seizures.

EXPERIMENTAL PROCEDURES

Study design

The overall experimental design is illustrated in Fig. 1. Seizures were induced in Sprague–Dawley rats at different ages from P1 to P90 by KA, PTZ or HT. Long-term structural and functional consequences of these seizures were assessed in adulthood using *ex vivo* DTI and MRI, *in vitro* electrophysiological recordings in hippocampal slices, and *in vivo* assessment of vulnerability to kindling. All rats in this study (n = 392) were housed and treated according to guidelines for the use of animals with institutional approval and oversight. Some of the data in this study have been previously presented in preliminary form (Sutula et al., 1992; Lynch et al., 2000; Hutchinson et al., 2012).

Seizure induction

Kainic acid. Seizures were induced by subcutaneous (SC) or intraperitoneal (IP) injection of KA at doses of 1–2-mg/kg (P1, P3, P7), 2–4-mg/kg (P14), or 8–10-mg/kg (> P24) based on previous studies of doses of KA that evoke SE in these age groups (Tremblay et al., 1984). In a subset of adult rats, KA was administered by intracerebroventricular (ICV) injection of 0.5–0.75 μg KA in 0.05–0.75 μL of deionized H_2O in rats anesthetized with pentobarbital (60-mg/kg) during a 15-min interval via a Hamilton syringe at 0.6 mm posterior, 2.0 mm lateral, and 3.5 mm ventral to bregma(Lynch et al., 2000). For all rats included in the study, behavioral seizures were classified by a modified Racine scale (Racine, 1972; Sutula and Steward, 1986) and were monitored for ~3–4 h to confirm that KA induced SE as classified by combined behavioral and electrographic criteria as in previous studies (Lynch et al., 2000). In P1, P3, and P7 rats that received 1–2-mg/kg KA IP, recurring seizures consisted of hyperactive "bicycling" movements of all extremities with opisthotonic arching of the back, and tonic limb extension. Administration of KA to P14 rats (2–4-mg/kg IP), and P20, P24, P31, P75 rats (8–10-mg/kg IP) reliably induced recurring behavioral seizures consisting of intermittent "freezing" or cessation of exploratory behavior, automatisms, salivation, tonic-clonic activities, and occasional loss of postural tone, which evolved into SE as reported previously. No significant differences in outcome measures were noted with systemic or ICV administration.

Pentylenetetrazol. Seizures were induced by PTZ (30-mg/kg IP) in subsets of rats on each of the following days: (P1, P5, P10), (P21, P24, P30), or every other day × 3 after ⩾P95. The evoked seizures included irregular myoclonic, tonic extension of limbs, and arching movements which lasted several minutes and did not recur, as described previously (Golarai et al., 1992).

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