

Temperature-Induced Reciprocal Activation of Hippocampal Field Activity

Karl Æ. Karlsson and Mark S. Blumberg

Program in Behavioral and Cognitive Neuroscience, Department of Psychology, University of Iowa, Iowa City, Iowa 52242

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Karlsson, Karl Æ. and Mark S. Blumberg. Temperature-induced reciprocal activation of hippocampal field activity. *J Neurophysiol* 91: 583–588, 2004. First published October 22, 2003; 10.1152/jn.00953.2003. Hippocampal network activity oscillates between sustained rhythms (e.g., theta) and aperiodic population spikes (e.g., sharp waves, dentate spikes). Although temperature is known to modulate various aspects of rhythmic hippocampal activity, little is known regarding the influence of temperature on the incidence of population spikes. We recorded spontaneous hippocampal activity along the CA1-dentate gyrus axis using multisite silicon electrodes in urethanized infant rats (P2–P16) at brain temperatures of 37 and 27°C. Theta and gamma activity, as well as sharp waves, were detected at 37°C but not at 27°C. In contrast, dentate spikes were rare at 37°C but their incidence increased several-fold at 27°C (epileptiform activity also emerged at 27°C in the oldest pups). This surprising increase in the incidence of dentate spike activity in a cold brain represents the first such demonstration for a neuronal field pattern. In addition, these findings indicate that changes in brain temperature produce systems-level shifts in the balance among reciprocally interacting hippocampal components.

INTRODUCTION

In adult rats, hippocampal network activity oscillates between two mutually exclusive modes: sustained rhythms, such as theta, and aperiodic population spikes, such as sharp waves and dentate spikes. The expression of these modes of activation is modulated by brain temperature, which affects virtually every aspect of neuronal function, including metabolism, enzymatic activity, ion channel kinetics, and axonal and synaptic transmission. For example, hippocampal theta rhythm is expressed only within a narrow thermal window and its dominant frequency (but not its amplitude) decreases with temperature (Kowalczyk et al. 2001; Weiss 1964; Whishaw and Vanderwolf 1971). In contrast, the amplitude of population spikes increases during cooling, likely due to differential thermal sensitivities of ion channels. Specifically, action potentials increase in duration and amplitude in the cold due to delayed activation of the potassium current; delayed repolarization results in larger spikes and more effective summation of spikes across neurons, thereby producing increased population spike amplitude (Andersen and Moser 1995).

Recently, developmental aspects of hippocampal activity and function have been gaining interest, with most studies using *in vitro* preparations (Ben-Ari 2001). Recognition of the need for assessing hippocampal function *in vivo* has been met with a spate of studies in the last several years (Karlsson and Blumberg 2003; Lahtinen et al. 2001; Leinekugel et al. 2002), producing some conflicting results. For example, using anes-

thetized and unanesthetized 3- to 6-day-old (P3–P6) rats, Leinekugel and colleagues (2002) reported that hippocampal field activity consists predominantly of sharp waves during the first postnatal week and that, consistent with a previous report in freely moving rats (Leblanc and Bland 1979), theta activity (as well as dentate spikes) is not detected until after P7. In contrast, it was reported recently that brief bursts of sleep-related theta activity can be detected in P2 rats (Karlsson and Blumberg 2003), a finding that may have been made possible by testing pups at thermoneutrality (i.e., 35°C). Specifically, testing pups at thermoneutrality could have influenced hippocampal activity through known effects of brain and body temperature on theta activity (Kowalczyk et al. 2001; Weiss 1964), active sleep (Sokoloff and Blumberg 1998), or both. This possibility highlights the need for systematic investigations of the thermal modulation of hippocampal field activity to complement similar studies at the neuronal level (Andersen and Moser 1995).

To further explore the relations of hippocampal activity and brain temperature, we used multisite silicon electrodes to record activity along the CA1-dentate gyrus axis in anesthetized P2–P16 rats while brain temperature was controlled at 37 and 27°C. We found robust temperature-dependent changes in field activity, including a surprising increase in the incidence of dentate spikes at 27°C; dentate spikes, first characterized in freely moving adult rats (Bragin et al. 1995), modulate excitability in the hippocampal formation (Bramham 1998; Penttonen et al. 1997). These findings indicate that changes in brain temperature produce systems-level shifts in the balance among reciprocally interacting hippocampal components.

METHODS

All experiments were performed under National Institutes of Health guidelines for the care of animals in research and were approved by the Institutional Animal Care and Use Committee of the University of Iowa.

Subjects

Fifteen P2–P16 male Sprague-Dawley Norway rats (*Rattus norvegicus*) from 12 litters were used. The pups were divided into three groups; P2–P5 ($n = 3$; 6.7–12.9 g body wt), P6–P10 ($n = 6$; 14.3–33.1 g body wt), and P12–P16 ($n = 6$; 32.2–44.0 g body wt). For a follow-up experiment, two additional P12 pups were used (32.2–34.4 g body wt). Litters were culled to eight pups within 3 days after birth (day of birth = Day 0). Mothers and their litters were housed in standard laboratory cages (48 × 20 × 26 cm) in the animal colony at the University of Iowa where food and water were available *ad libitum*. All animals were maintained on a 12:12 h light-and-dark

Address for reprint requests and other correspondence: M. S. Blumberg, Dept. of Psychology, E11 Seashore Hall, University of Iowa, Iowa City, IA 52242 (E-mail: mark-blumberg@uiowa.edu).

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schedule with lights on at 07:00 h. All experiments were conducted during the lights-on phase.

Procedure and data acquisition

On the day of testing, a pup with a visible milk band was removed from the litter, weighed, and injected with urethan (1.5–2.0 mg/g ip). When needed, urethan was supplemented in small increments (0.05 mg/g) until the pedal reflex could not be elicited. When a surgical level of anesthesia was attained, the pup was secured in a stereotax with modified ear bars (David Kopf Instruments, Tujunga, CA). The pup rested on a radiator assembly through which temperature-controlled water was circulated. A silver reference electrode was placed in the cortex anterior to bregma, a small piece of skull (1 mm²) over the dorsal hippocampus was removed, the dura retracted, and a 16-site silicon recording electrode (100- μ m vertical separation between recording sites; University of Michigan Center for Neural Communication Technology) was positioned over the exposed surface of the brain. Forty-gauge copper-constantan thermocouples (Omega Engineering, Stamford, CT) were placed in the rectum and brain; placement within the brain was ~2 mm anterior to bregma, 2 mm lateral to midline, and 3 mm beneath the cortical surface. Pilot experiments indicated that brain temperature measured at this location was within 0.1°C of that measured at the site of electrode placement.

Maintenance of rectal temperature at 37°C is not sufficient to control brain temperature at 37°C in adult rats (Andersen and Moser 1995), and this is particularly true in infants. Therefore in addition to the temperature-controlled radiator, the pup's brain temperature was controlled using a heat lamp. When brain temperature had stabilized at 36–38°C, the electrode was inserted under electrophysiological guidance into the CA1-dentate gyrus ($n = 13$) or CA1–CA3 ($n = 2$) axis (see Fig. 1E). When the electrophysiological signals had stabilized, a 5-min period of data collection began. Then, the heat lamp and radiator were adjusted so as to decrease brain temperature to 25–30°C, at which time a second 5-min period of data collection began. Finally, the pup's brain temperature was increased to 36–38°C and the final 5-min period of data collection began. In all cases, the recording took place only after electrophysiological signals and temperature had been stable for ≥ 10 min.

The silicon electrode was connected to a unity-gain headstage that, in turn, was connected to a digital amplifier (Tucker-Davis Technologies, Alachua, FL). Signals were amplified ($\times 10,000$) and filtered (using either a 5,000-Hz low-pass or a 1- to 5,000-Hz band-pass filter) before being sampled at 12.5 kHz using a digital interface (Cambridge Electronic Design, Cambridge, UK). All data were recorded to hard disk for off-line analysis using Spike2 software (Cambridge Electronic Design).

Brain and rectal temperatures were sampled using a thermocouple temperature meter (Sable Systems International, Las Vegas, NV) and acquired in synchrony with the neurophysiological signals.

At the end of the experiment, two small marking lesions were made by passing 50- to 75- μ A anodal current through the deepest electrode for 3–6 s, followed by a second lesion after withdrawing the electrode 1.0 or 1.6 mm. The pup was overdosed with pentobarbital sodium and perfused through the heart with saline and formalin. Heads were postfixed with a sucrose-formalin solution for 24 h, whereupon the brain was removed and postfixed for ≥ 48 h. Brains were sliced in the coronal plane into 50- μ m sections, mounted, and stained with cresyl violet to identify the location of the lesions.

Data analysis

For each pup, a 5-min segment from each of the recording phases was inspected and four categories of hippocampal activity were scored: phasically occurring dentate spikes and sharp waves, bursts of sustained activity that contained waves in the theta and gamma range as well as large-amplitude irregular activity (LIA), and epileptiform

activity. The occurrence, duration, and amplitude of each event were recorded and entered into Statview 5.0 (SAS, Cary, NC) for statistical analysis.

Rhythmic/LIA was defined as a burst of theta activity, gamma activity, and/or LIA with a peak amplitude at least twice the baseline amplitude. Sharp waves were defined as high-amplitude, short-duration (30–120 ms) events that exhibited a phase reversal across the CA1 pyramidal layer (see Fig. 1, A and D), going from positive to negative with the negative maximum in the stratum radiatum (peak negative amplitude ≥ 3 times the noise band). Epileptiform activity was defined as negative-going, high-amplitude, synchronous spiking. Epileptiform activity was easily distinguished from other activity patterns on the basis of its form, arrhythmia, and by the fact that it is duplicated with little change throughout many layers along the CA1-dentate gyrus axis, showing no reversal in phase (see Fig. 1B). Finally, dentate spikes were defined as high-amplitude, short-duration (15–50 ms) events that exhibited a phase reversal across the granule cell layer (see Fig. 1, C and D), going from negative to positive, with the positive maximum at the hilar region (peak positive amplitude ≥ 5 times the noise band). No attempt was made to distinguish between the DS1 and DS2 subclasses of dentate spikes (Bragin et al. 1995; Bramham 1998).

The incidence of sharp waves and dentate spikes, and the duration of rhythmic/LIA and epileptiform activity, were quantified for each age group at 37, 27, and again at 37°C. Because there were no differences in any measure between the first and second tests at 37°C, these data were averaged before analysis. A two-factor ANOVA, with age group and brain temperature as factors, was used. Paired *t*-tests were used for post hoc comparisons. For all tests, alpha was set at 0.05.

Unit activity in the CA1 pyramidal cell layer and field activity in s. radiatum before and after a dentate spike were examined in depth in one P16 subject. A recording from the CA1 pyramidal field was filtered for unit activity (500–5,000 Hz) and individual spikes were sorted and counted using Spike2 software. Pyramidal cell firing rates were measured in 100-ms bins over a 2-s period for each of 37 individual dentate spikes for this subject. Finally, a peristimulus histogram of CA1 multiunit activity, with each dentate spike as the trigger, was created.

RESULTS

Absence of hippocampal activity in urethanized P2–P5 rats

Contrary to expectations, no discernable hippocampal activity was observed before P6. At P2–P5, the EEG was virtually silent and did not show any activity-related changes as a function of temperature. Thus P2–5 rats were not included in any of the subsequent analyses.

Theta, gamma, and large irregular activity (rhythmic/LIA)

Beginning at P6, silence in the hippocampal electroencephalogram (EEG) was broken by bursts of activity composed of rhythmic theta and gamma activity as well as large irregular activity (LIA; Fig. 1A). Although urethanized adult rats oscillate between two hippocampal states—theta/gamma and LIA (including dentate spikes and sharp waves)—infant rats oscillate between states of relative EEG quiescence and brief bursts of activation comprised of theta/gamma waves and LIA. Therefore rhythmic activity (i.e., theta/gamma) and LIA were analyzed together. The number of bursts, and the duration of each burst, increased with age. As a result, total duration of rhythmic/LIA increased with age (Fig. 3A). Moreover, Fig. 2A shows that this activity was only detected at brain temperatures of 37°C. Observations during each test suggested that, in

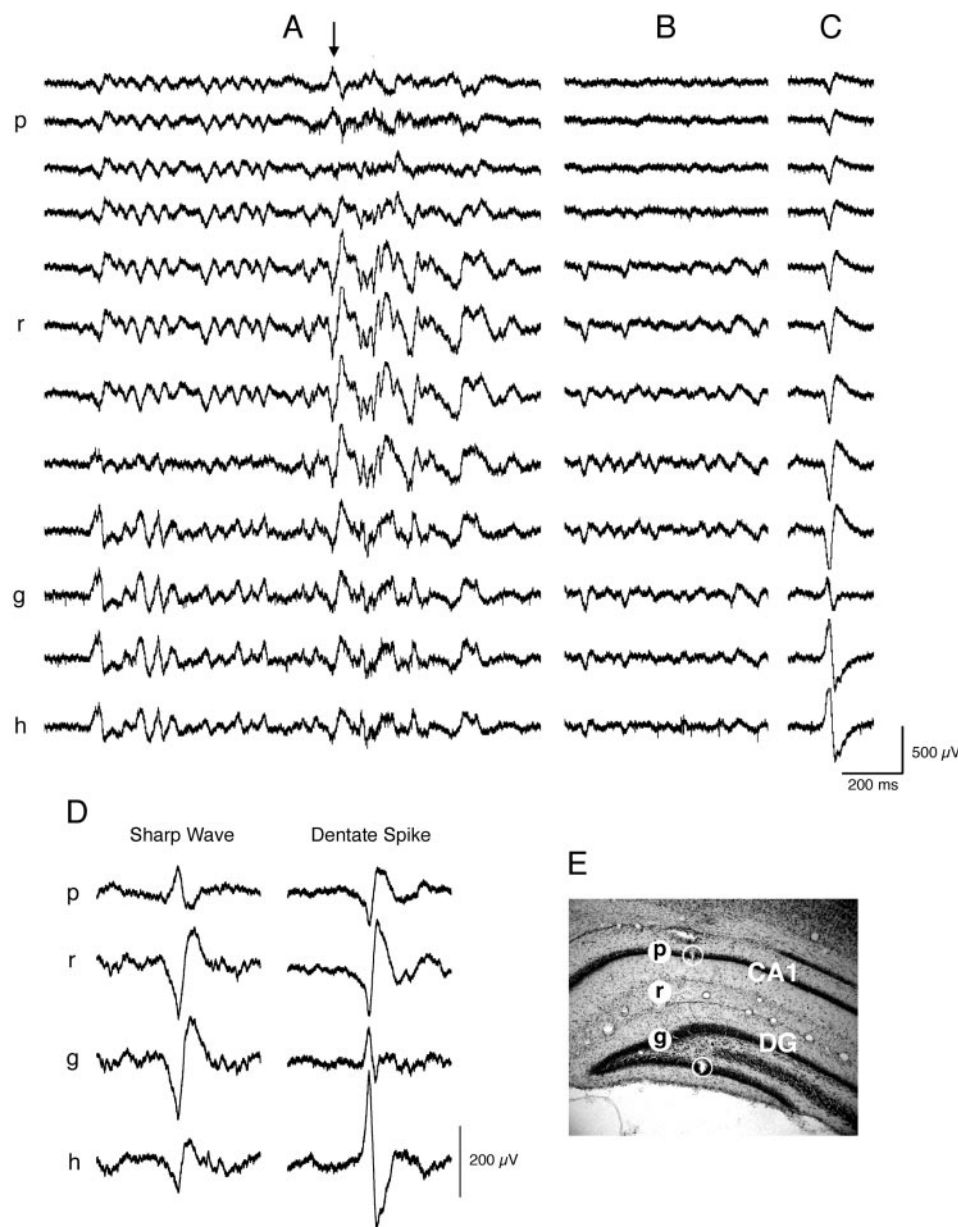


FIG. 1. Examples of hippocampal field activity in a P12 rat. *A*: a burst of rhythmic/large-amplitude irregular activity (LIA) recorded at a brain temperature of 37.6°C. ↓, the occurrence of a sharp wave that, in this instance, is embedded within the burst (sharp waves also often occurred as isolated events); note the phase reversal across the pyramidal cell layer. *B*: epileptiform activity recorded at a brain temperature of 28.6°C; note the absence of phase reversals. *C*: a dentate spike recorded at a brain temperature of 28.6°C; note the phase reversal across the granule cell layer. For ease of comparison, signals in A–C are filtered identically (low-pass = 5,000 Hz). Also, they are presented on the same temporal and amplitude scales. Adjacent electrode sites are 100 μm apart. *D*: averaged sharp waves and dentate spikes from the same P12 rat ($n = 10$ events/trace) at a brain temperature of 37.4°C. Only selected electrode channels are shown. All signals are 400 ms in duration and are filtered identically (low-pass = 5,000 Hz). *E*: photomicrograph of the infant hippocampal formation. Marking lesions showing the axis of the silicon electrode are indicated with white circles (~ 1 mm apart). In this subject, the dorsal lesion was made in the pyramidal cell layer and the ventral lesion was made in the lower blade of the dentate gyrus. p, pyramidal cell layer; r, stratum radiatum; g, granule cell layer; h, hilar region; DG, dentate gyrus.

P6–P8 subjects, rhythmic/LIA decreased gradually with brain temperature until it disappeared at $\sim 33^\circ\text{C}$; in older subjects, greater brain cooling was required to eradicate rhythmic/LIA. ANOVA revealed significant main effects of age [$F(1,20) = 12.9$, $P < 0.005$] and temperature [$F(1,20) = 22.2$, $P < 0.0001$] and a significant age \times temperature interaction [$F(1,20) = 12.7$, $P < 0.005$].

Sharp waves

Although detectable beginning at P6, sharp waves (Fig. 1A) occurred rarely and at similar rates in all age groups. As with rhythmic/LIA, they were most prominent when brain temperature was 37°C (Fig. 2B). ANOVA revealed only a significant main effect of temperature [$F(1,20) = 17.0$, $P < 0.0005$]. CA1 pyramidal layer “ripples,” which accompany sharp waves in adults (Buzsáki et al. 1992) but not infants (Leinekugel et al. 2002), were not detected at any age. Finally, averaged traces of

sharp waves (Fig. 1D) resemble records previously reported in infant rats (Leinekugel et al. 2002).

Epileptiform activity

Epileptiform activity, characterized by nonrhythmic, negative-going spikes occurring synchronously (i.e., without phase reversals) throughout many layers of the hippocampus (Fig. 1B), first became prominent at P12 and only at a brain temperature of 27°C (Fig. 2C). ANOVA revealed significant main effects of age [$F(1,20) = 5.2$, $P < 0.05$] and temperature [$F(1,20) = 5.3$, $P < 0.05$] and a significant age \times temperature interaction [$F(1,20) = 5.2$, $P < 0.05$].

Dentate spikes

Characterized by a sharp phase reversal across the granule cell layer (Fig. 1C), dentate spikes occurred with a similar

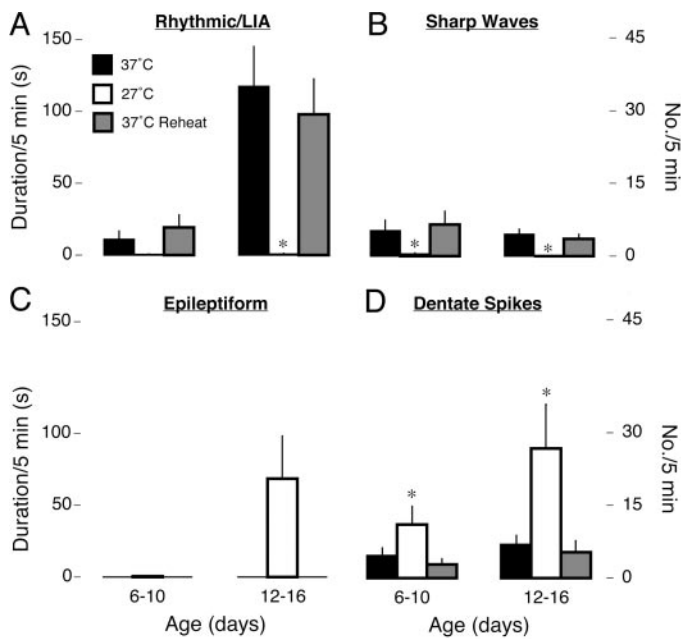


FIG. 2. Hippocampal field activity as a function of age and brain temperature. Recordings were made at a brain temperature of 37, 27, and again at 37°C. *A*: mean cumulative duration of rhythmic/LIA per 5 min. *B*: mean number of sharp waves per 5 min. *C*: mean cumulative duration of epileptiform activity per 5 min. *D*: mean cumulative number of dentate spikes per 5 min. $n = 6$ for each age group. Mean + SE. *, significantly different from the mean of the values at 37°C, $P < 0.05$, paired t -test.

frequency as sharp waves at a brain temperature of 37°C; these events occurred aperiodically and were interspersed with sharp waves and LIA. In contrast, dentate spikes occurred with much greater frequency when brain temperature was decreased to 27°C (Fig. 2*D*). ANOVA revealed only a significant main effect of temperature [$F(1,20) = 7.6$, $P < 0.05$]. Finally, averaged traces of dentate spikes (Fig. 1*D*) resemble records previously reported in adult rats (Bragin et al., 1995).

Incidence of sharp waves and dentate spikes during brain cooling

Observations of sharp wave and dentate spike activity during brain cooling indicated that changes occurred gradually. To document this phenomenon, two additional P12 rats were tested using the same procedure described in the preceding text except data were recorded continuously as brain temperature decreased. Sharp waves and dentate spikes were counted as described previously within each of five temperature ranges between 27 and 37°C and averaged across the two subjects. As shown in Fig. 3, during brain cooling, the incidence of sharp waves decreased gradually and the incidence of dentate spikes increased gradually. When examined individually, there was no evidence of a threshold temperature at which hippocampal activity changed abruptly from one state to another.

Dentate gyrus-CA1 field interactions

The effect of dentate spikes on the activity of CA1 pyramidal cells and epileptiform activity was examined in depth in a P16 subject that exhibited robust unit activity in the CA1 pyramidal layer under cold conditions. Inspections of unit activity in CA1 and field activity in s. radiatum indicated an

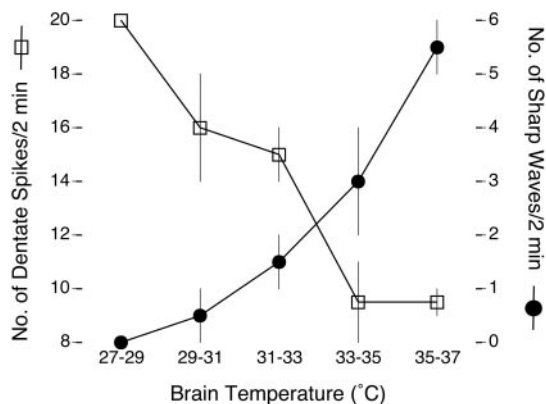


FIG. 3. Gradual changes in the incidence of dentate spikes and sharp waves in response to decreasing brain temperature in P12 rats. Data were collected from 2 subjects over a 30-min test session in which brain temperature was decreased from 37 to 27°C. For each subject, dentate spikes and sharp waves were counted over 2 min within each temperature range depicted on the graph and averaged across subjects. Mean ± SE.

association between dentate spikes and suppression of pyramidal cell and epileptiform activity (Fig. 4*A*). A peristimulus histogram for 37 dentate spikes revealed that this pattern was reliable (Fig. 4*B*). CA1 units were inhibited in conjunction with dentate spikes and for 200–400 ms thereafter. In instances where a dentate spike was preceded by epileptiform activity, that activity was also suppressed (see Fig. 4*A*, bottom).

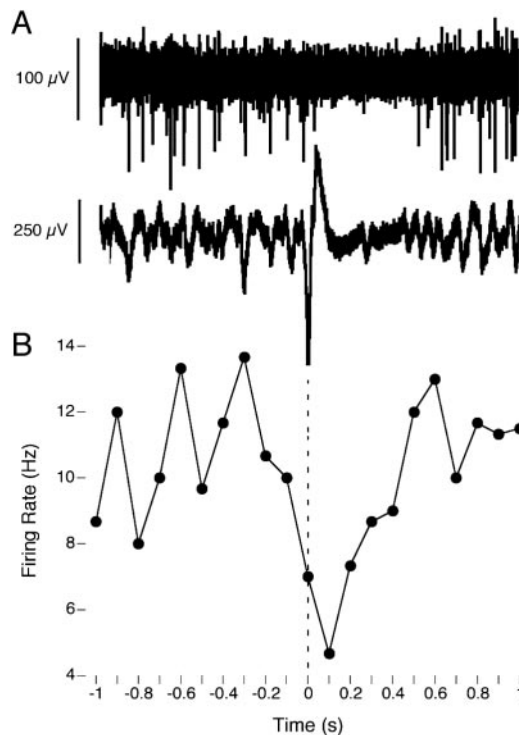


FIG. 4. Dentate spikes suppress CA1 unit activity. *A*: 2 concurrent traces depicting pyramidal cell activity filtered to reveal spike activity in CA1 pyramidal cells (500–5,000 Hz; top) and field activity in stratum radiatum (1–5,000 Hz, bottom). A biphasic dentate spike, evident in the bottom trace at time 0, is preceded by epileptiform activity. *B*: peristimulus histogram showing average firing rates across a 2-s window for 37 dentate spikes (triggered at time 0) for the same rat as in *A* (bin size = 100 ms). Data are from a P16 rat. Time scale is the same for all plots. Brain temperature = 28.8°C.

DISCUSSION

This is the first report of infant hippocampal field activity *in vivo* in which brain temperature was explicitly controlled. Consistent with work in adults (Weiss 1964; Whishaw and Vanderwolf 1971), we found that theta activity was reversibly abolished at low brain temperatures; in addition, other forms of hippocampal activity, including gamma, LIA, and sharp waves, were abolished. In contrast, epileptiform activity emerged during brain cooling, although only in the older infants; cold-induced epileptiform activity has also been described *in vitro* (Kowalczyk et al. 2001). Most surprisingly, however, the number of dentate spikes increased dramatically in the cold. To our knowledge, this is the first demonstration of cold-induced augmentation of a nonpathological hippocampal field pattern.

When an infant rat is isolated at thermoneutrality (35°C), core temperature (including brain temperature) is maintained at ~37°C; under these conditions, the predominant behavior is active sleep (Blumberg and Stolba 1996; Karlsson and Blumberg 2002). During cooling to subthermoneutral air temperatures, pups produce heat primarily through sympathetic activation of brown adipose tissue (BAT). BAT thermogenesis increases in lock-step with decreasing air temperature until, at ~25°C in 1-wk-old rats, it can increase no further. At this transition from moderate to extreme cooling, with a core temperature of ~35°C, pups exhibit a variety of behavioral and physiological responses including prolonged periods of wakefulness, decreased cardiac rate, and emission of ultrasonic vocalizations (Blumberg 2001). After 1–2 h at room temperature (18–22°C), with core temperature falling to levels <27°C, pups continue to vocalize while exhibiting high levels of activity (Blumberg et al. 1999; Sokoloff and Blumberg 1998). In pups that cannot produce heat using BAT (e.g., after starvation) or in species in which BAT thermogenesis is developmentally delayed (e.g., hamsters), core temperature decreases even more rapidly in the cold (Blumberg 2001). Thus a brain temperature of 27°C is well within the range of temperatures likely experienced by infant altricial rodents during prolonged maternal absence or disturbances of the nest (e.g., by flooding) (Calhoun 1962).

Based on the findings from the initial study reporting the discovery of dentate spikes (Bragin et al. 1995) and from a subsequent study (Penttonen et al. 1997), it was concluded that dentate spikes produce feedforward excitation of dentate granule cells (from entorhinal cortex via the perforant path) and that sharp waves produce feedback excitation of granule cells (via CA3 projections to the dentate gyrus). But although dentate spikes and sharp waves share the feature of granule cell excitation, these two events have opposite effects on excitability elsewhere in the hippocampus. This balanced reciprocity between dentate spikes and sharp waves has been revealed by cutting off entorhinal input to the hippocampus in adult rats, thereby abolishing dentate spikes and increasing the number of sharp waves (Bragin et al. 1995). The present results support and extend these findings by demonstrating that changes in brain temperature can modulate the reciprocal interactions among hippocampal and/or extrahippocampal components, tipping the balance toward dentate spikes or toward sharp waves, theta/gamma, and LIA (see Figs. 2 and 3). Although much is known regarding thermal modulation of hippocampal activity at the neuronal and population levels (Andersen and Moser

1995), an explanation for the differential thermal sensitivity of hippocampal components at the systems level is not readily apparent.

The absence of discernible hippocampal activity at P2–P5 reported here is not consistent with a previous report using similar methods (Leinekugel et al. 2002). In that study, urethanized P3–P6 rats were reported to exhibit hippocampal activity composed exclusively of sharp waves; in contrast, we did not detect sharp waves until P6, and they were never more prominent than other hippocampal field patterns. Although brain temperature was not explicitly controlled in the Leinekugel et al. study, a cold brain likely would have decreased, not increased, the number of sharp waves reported (see Fig. 2). Therefore there is no obvious explanation for this discrepancy. On the other hand, the two studies are largely in agreement regarding the developmental emergence of theta/gamma, LIA, and dentate spikes under anesthesia.

A comparison of hippocampal activity in anesthetized (this study, see Fig. 2) and unanesthetized (Karlsson and Blumberg 2003) infant rats suggests that the earliest detectable theta is suppressed by urethane. Specifically, in P2–P4 rats tested in a thermoneutral environment and exhibiting normal cycling between sleep and wakefulness, we detected many instances of brief bursts of theta activity associated with active sleep (Karlsson and Blumberg 2003). Brief theta bursts have also been reported in adult rats during active sleep and, significantly, these bursts are abolished by urethane (Robinson et al. 1977). Thus it is possible that the urethane-sensitive type of theta emerges earlier in development in rats than the urethane-resistant type of theta [as is the case in rabbits (Creery and Bland 1980)] and, as a consequence, the neonate's hippocampal activity is relatively quiet under urethane. Alternatively, because the youngest pups tested here (i.e., P2–P5) required a higher dose of urethane to reach a surgical plane of anesthesia, it is possible that urethane resulted in greater suppression of hippocampal activity at these ages.

The functional consequences of brain temperature have been well studied in the hippocampus (Andersen and Moser 1995; Schiff and Somjen 1985; Thompson et al. 1985), in part because of this forebrain structure's established role in learning and memory (Eichenbaum 2000; O'Keefe and Nadel 1978). Surprisingly, even decreases in brain temperature to 30°C, which slow all field activity within the dentate gyrus, do not interfere with a rat's ability to learn a hippocampal-dependent spatial learning task (Moser and Andersen 1994). It has been proposed that dentate spikes represent a natural mechanism for generating plastic changes at mossy fiber-CA3 synapses by boosting excitatory input from the entorhinal cortex (Bramham 1998). If the present results in anesthetized infants are mirrored in freely moving adults, the increased number of dentate spikes during hypothermia may offer a mechanism by which hippocampal function is conserved at low temperatures.

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