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Cooling Abolishes Neuronal Network Synchronization in Rat Hippocampal Slices

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Summary: *Purpose:* We sought to determine whether cooling brain tissue from 34 to 21°C could abolish tetany-induced neuronal network synchronization (gamma oscillations) without blocking normal synaptic transmission.

Methods: Intracellular and extracellular electrodes recorded activity in transverse hippocampal slices (450–500 μm) from Sprague–Dawley male rats, maintained in an air–fluid interface chamber. Gamma oscillations were evoked by afferent stimulation at 100 Hz for 200 ms. Baseline temperature in the recording chamber was 34°C, reduced to 21°C within 20 min.

Results: Suprathreshold tetanic stimuli evoked membrane potential oscillations in the 40-Hz frequency range (n = 21). Gamma oscillations induced by tetanic stimulation were blocked by bicuculline, a γ-aminobutyric acid (GABA)$_A$-receptor antagonist. Cooling from 34 to 21°C reversibly abolished gamma oscillations in all slices tested. Short, low-frequency discharges persisted after cooling in six of 14 slices.

Single-pulse–evoked potentials, however, were preserved after cooling in all cases. Latency between stimulus and onset of gamma oscillation was increased with cooling. Frequency of oscillation was correlated with chamber cooling temperature (r = 0.77). Tetanic stimulation at high intensity elicited not only gamma oscillation, but also epileptiform bursts. Cooling dramatically attenuated gamma oscillation and abolished epileptiform bursts in a reversible manner.

Conclusions: Tetany-induced neuronal network synchronization by GABA$_A$-sensitive gamma oscillations is abolished reversibly by cooling to temperatures that do not block excitatory synaptic transmission. Cooling also suppresses transition from gamma oscillation to ictal bursting at higher stimulus intensities. These findings suggest that cooling may disrupt network synchrony necessary for epileptiform activity. **Key Words:** Epilepsy—Hippocampus—Cooling—Hypothermia—Synchronization.

Focal cooling has been suggested as a treatment for epilepsy. In vivo experiments confirmed that cooling reversibly inactivates mammalian cortex (1–4). Clinical case reports have documented use of cooling in a variety of epileptic conditions (5–10). Recent studies in hippocampal slices and in whole rats showed that rapid cooling to 22.0°C can halt seizure activity induced by 4-aminopyridine (11,36). Rapid cooling also blocked single-pulsed–evoked potentials in dentate granule cell layer neurons.

Mechanisms of cooling as an antiepileptic therapy remain unknown. Tetany-induced discharges in the range of 30–120 Hz, also called gamma oscillations, resemble spontaneous oscillations seen under a variety of epileptic conditions (12). These oscillations reflect network synchronization mediated by γ-aminobutyric acid

(GABA)$_A$-ergic depolarizations. Gamma oscillations recently have been identified *in vitro* in slice models of epilepsy. They are seen in transition to epileptiform bursting, spontaneously and in response to single-pulse stimulation in low-Mg^{2+} conditions, after high-frequency tetanic stimulation, and in juvenile slices subjected to hyperthermia in a febrile seizure model(12,13). In this study, we provide evidence that cooling disrupts epileptiform activity, at least in part, by blocking gamma oscillations.

MATERIALS AND METHODS

Transverse hippocampal slices (450–500 μm) were prepared from juvenile (postnatal days 14–30) and adult (>30 days old) Sprague–Dawley rats (n = 21). Rats were anesthetized with halothane and then decapitated. The brain was placed into an oxygenated Ringer's solution at 10°C, mounted on a vibratome, and 450-μm slices were cut. Slices were incubated at room temperature for ≥60

min, and then maintained in an interface chamber at 32–35°C. Artificial CSF (aCSF) containing (in m*M*): NaCl, 117; KCl, 5.4; NaHCO$_3$, 26; MgSO$_4$, 1.3; NaH$_2$PO$_4$, 1.2; CaCl$_2$, 2.5; glucose, 10 was bubbled with 95% O$_2$ and 5% CO$_2$. Blunt glass micropipettes filled with NaCl were used to record field potential from CA1 and sharp glass micropipettes (70–120 MΩ) filled with potassium acetate were used for intracellular recordings. For single-pulse–evoked potentials, Schaffer collaterals were stimulated with a bipolar platinum wire electrode for 100 μs. Recordings were made from stratum pyramidale in CA1 by a field and an intracellular electrode. For tetany–induced discharges, stimulation was changed to a train of 100 Hz for 200 ms.

Recordings were made only after ≥60 min of incubation at room temperature, followed by ≥30 min at control temperature (32–34°C) in the interface chamber. Temperature was controlled by using a thermostat with feedback from a temperature sensor (Fine Science Tools, Inc., Foster City, CA, U.S.A.). Previous experiments used a sensor connected to a probe penetrating the slice. After demonstrating excellent temperature correlation with only a small time delay (data not shown), a less cumbersome probe positioned just under the interface chamber was used for these experiments. Cooling was aided by continuously exchanging water in the chamber water jacket.

Cooling experiments (n = 21) were initiated at 32–34°C. Cooling to ~21°C was accomplished within 20 min. The water bath in the slice chamber was slowly recirculated with ice water and the aCSF replaced with aCSF precooled to 4°C. Recordings were made every 3 min during cooling. Single-pulse–evoked potentials were measured first, and then tetanic stimulus was delivered. Stimulus intensity was kept constant through the cooling and rewarming. Stimulus intensities just above threshold to produce gamma oscillations (usually 1.25–2.25 mA) were used in 14 slices. Higher intensities (150–200% of threshold) were used to elicit gamma oscillations, followed by ictal bursts in five slices.

Analysis was performed off-line by using spike-counting software (Origin pClamp). Initial frequency for an oscillation was defined as the spike frequency during the first 250 ms of the oscillation. Latency was defined as the time between the offset of the stimulus and the first spike of the oscillation. For single-pulse–evoked potentials, amplitude was measured in the following way: A line was drawn connecting the peaks of the two positive deflections in the population spike. The distance from the midpoint of this line to the trough of the negative deflection was measured as the amplitude. Half-time durations were measured by drawing a line perpendicular to the amplitude line at its midpoint. The duration between the two points where the potential tracing crossed this line was the half-time duration, a reflection of the width of the waveform.

RESULTS

Single-pulse–evoked field potentials were not blocked by cooling

Single 100-μs pulses evoked field potentials under control conditions and after cooling in all of the slices. In no cases was the potential blocked with cooling to as low as 21°C. Amplitude of the single-pulse–evoked potential showed no statistically significant change with cooling (p = 0.36, NS). However, the duration at the midpoint of the evoked field increased with cooling (0.89 vs. 2.14 ms; p = 0.00002). The amplitude ratio from slices at the lowest temperature compared with those at control temperature ranged from 0.64 to 1.58 (mean, 0.96; SD, 0.31).

Gamma oscillations are associated with epileptiform conditions

Certain aspects of epilepsy have been modeled by using hippocampal slices perfused by very low magnesium solutions (14). In three of three slices tested, withdrawal of magnesium led to increased population spike amplitude, followed by an oscillation of multiple spikes in the 40- to 44-Hz range (mean, 42.7 Hz) in response to a single 100-μs stimulus. The duration of the oscillation was 401 to 586 ms (mean, 485 ms). The oscillation was followed by ictal bursts in one of three slices. Intracellular recordings demonstrated an oscillation consisting of action potentials in the 36- to 60-Hz range (mean, 45.3 Hz) during a transient depolarization. These responses disappeared on reperfusion with magnesium-containing perfusate.

High-frequency tetanic stimulation provided a model for this ictal synchronization. Figure 1 shows the similarity between the oscillation generated by high-frequency tetanic stimulation and that generated by a single-pulse stimulus in the same hippocampal slice after 60 min of exposure to magnesium-free perfusate.

γ-Aminobutyric acid type A (GABA$_A$) inhibition blocks this ictal hypersynchrony while causing hyperexcitability

Tetanic stimulation elicited discharges in nine of nine slices tested. In all instances, the discharges were blocked reversibly by 10 μ*M* bicuculline (Fig. 2).

Tetany-induced discharges are blocked reversibly by cooling

Tetanic stimulation was used to elicit oscillations in hippocampal slices. Typical oscillations started a mean of 186 ms (n = 4) after stimulus under control conditions. Oscillations lasted 331–4,200 ms (mean, 1,288; SD, 1,045 ms). The frequency of the afterdischarge was initially in the gamma oscillation range, and typically

FIG. 1. Recordings from a CA1 pyramidal neuron and field in response to high-frequency tetanic stimulation (left), after a single 100-μs pulse (middle), and after a single 100-μs pulse after 60 min in low-magnesium perfusate (right).
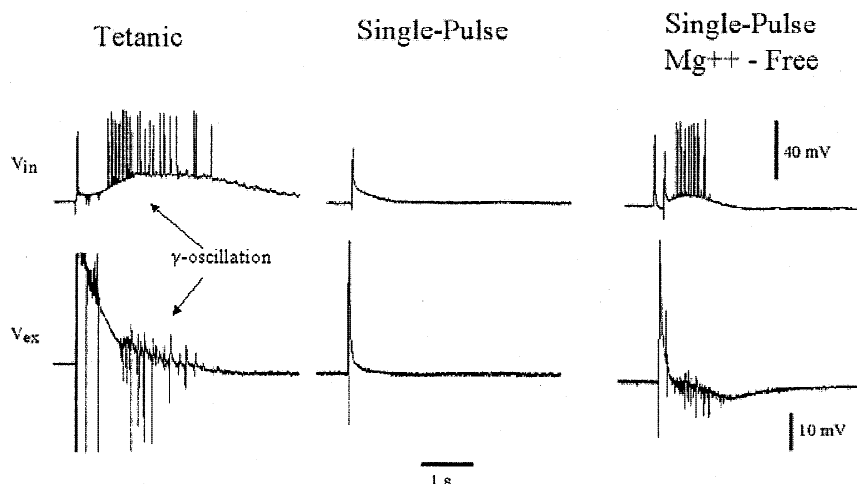
decreased with time. Mean initial frequency of each oscillation was 40 Hz (mean, 40 Hz; SD, 10.3 Hz; range, 16–60 Hz).

Figure 3 shows the typical changes in field and intracellular recordings during cooling and rewarming.

Pooled data (Fig. 4) show that initial frequency decreased with temperature in an approximately linear relation (R = 0.77; SD, 0.24; linear fit equation, Y = 0.088X − 1.7). Latency increased consistently with temperature, although the magnitude of the increase was different for each slice. Mean latency increased from 186 ms under control conditions to 763 ms after cooling (p = 0.000002). Figure 4B shows an accelerating increase in latency with decreasing temperature. Both changes in the initial frequency of the oscillation and in the latency were reversible on rewarming in all slices. Slices (n = 3) maintained at 21°C for 30 min did not adapt; the oscillation remained blocked, and recovery was still possible with rewarming in all three slices.

Cooling blocked ictal bursts elicited by higher stimulation intensity

Increasing the intensity of high-frequency tetanic stimulation to 150–200% of threshold led to ictal-like bursts (Fig. 5A), seen in 13 of 26 of slices tested with progressively higher-intensity tetanic stimuli. Multiple bursts (mean, 3.0; range, 1–8; SD, 2.1) had mean duration of 171 ms and increased after a mean delay of 960 ms after the initial oscillation. In six of 13 slices, bursts were followed by a spreading depression (*not shown*).

In five slices, we observed the effects of cooling on gamma oscillations and subsequent ictal-like bursts produced by tetanic stimulation at 200% of threshold. On cooling these slices, bursts disappeared in all slices tested, and gamma oscillations were reduced in frequency (Fig. 5B). The bursts returned on rewarming in all cases. In two of five slices on rewarming, the bursts returned and were followed by spreading depressions. Single-pulse–evoked potentials were not blocked

FIG. 2. Recordings from a CA1 pyramidal neuron (V_in) and field potential (V_ex) after a single 100-μs pulse **(A)** and after 100-ms tetanic pulse **(B)** to Schaffer collaterals, under control conditions and after exposure to 10 μM bicuculline for 15, 20, and 30 min, which suppresses the gamma oscillation while increasing excitability to a single-pulse stimulus. Synchronization was suppressed at the same time that excitability increased, as reflected by the development of multiple population spikes in the same slice with increasing time of exposure to bicuculline. In addition to multiple population spikes, slices exposed to 10 μM bicuculline developed increased spontaneous activity.
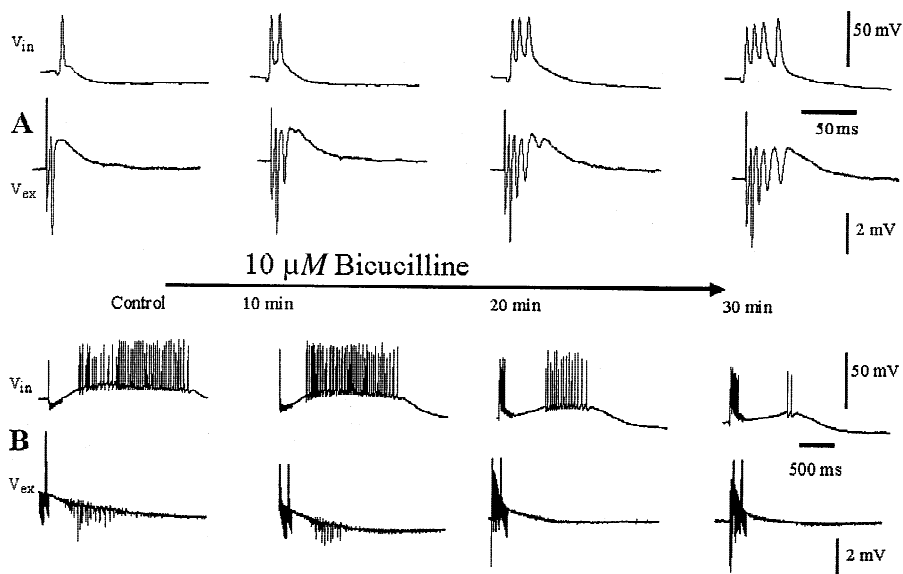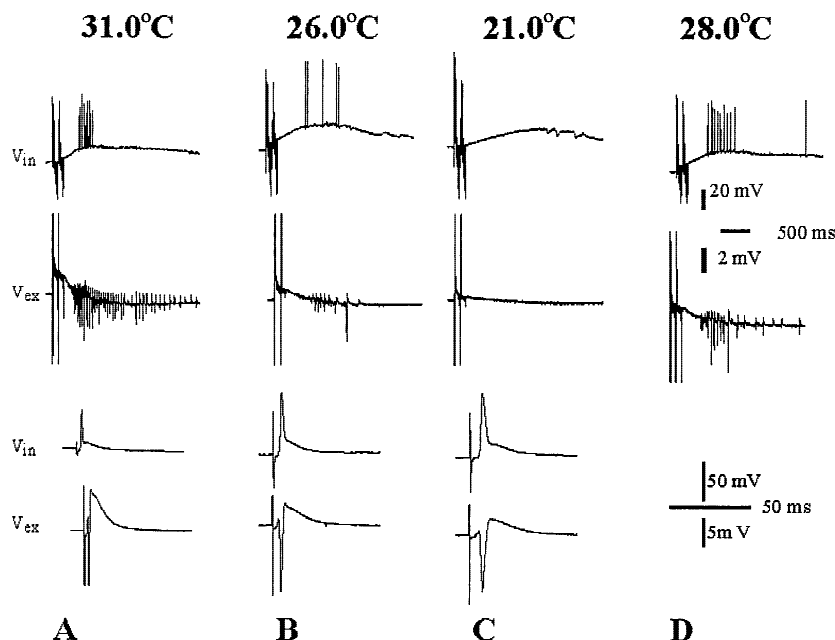
FIG. 3. Typical series of recordings during cooling **(A–C)** and rewarming **(D)** demonstrates reversible suppression of the gamma oscillation without abolishing single-pulse responses (*inset*). Oscillation frequency usually began to decrease at 27°C. With lower temperatures, frequencies continued to decline, and oscillations were eliminated at ~21°C. Discharges were completely abolished in eight of 14 and reduced to subfrequency in six of 14. Oscillation frequency after cooling was 3.2 Hz (mean, 3.2; SD, 3.52; range, 0–8 Hz).

at the temperature required to abolish the ictal-like bursts.

Cooling changed bicuculline-induced epileptiform bursting

We performed cooling experiments on five slices after perfusion with 10 μM bicuculline. Cooling changed the multiple-population spike to a more prolonged response, sometimes with fewer multiples. Amplitude did not change significantly, and the population spike was never blocked (Fig. 6).

DISCUSSION

In this study, we showed that cooling hippocampal slices blocked synchronous high-frequency activity, known as gamma oscillations. Tetanic stimulation pro-

duced ictal-like bursts after gamma oscillations in about half of the tested slices; cooling also abolished these ictal-like bursts.

Posttetanic oscillations as an in vitro model of epilepsy

Several prior studies used gamma oscillations to model seizures, although such oscillations variably have been termed "paroxysmal after-discharges" (15), "synchronized burst discharges" (16), and "gamma-oscillations" (12). These oscillations display a tonic period of rapid firing, during which intracellular recordings reveal strong depolarizations and extracellular recordings show negative shifts (15). Oscillations may be followed by a series of rhythmic bursts, depending on the intensity and frequency of the tetanic stimulus (15).
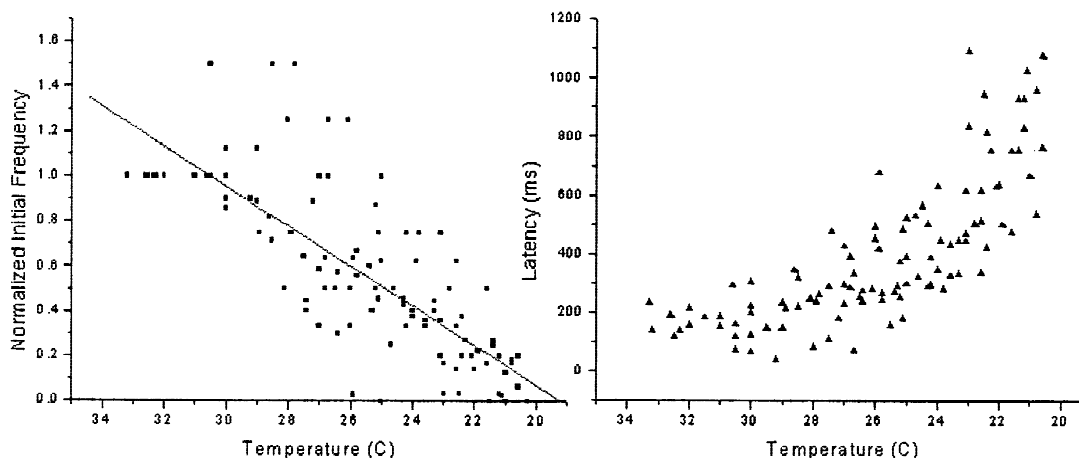

FIG. 4. Pooled data from CA1 field recordings in 14 slices during cooling. Initial frequency during the first 250 ms of the oscillation decreases linearly with cooling (R = 0.77; SD, 0.24; p < 0.0001), and latency increases with cooling.
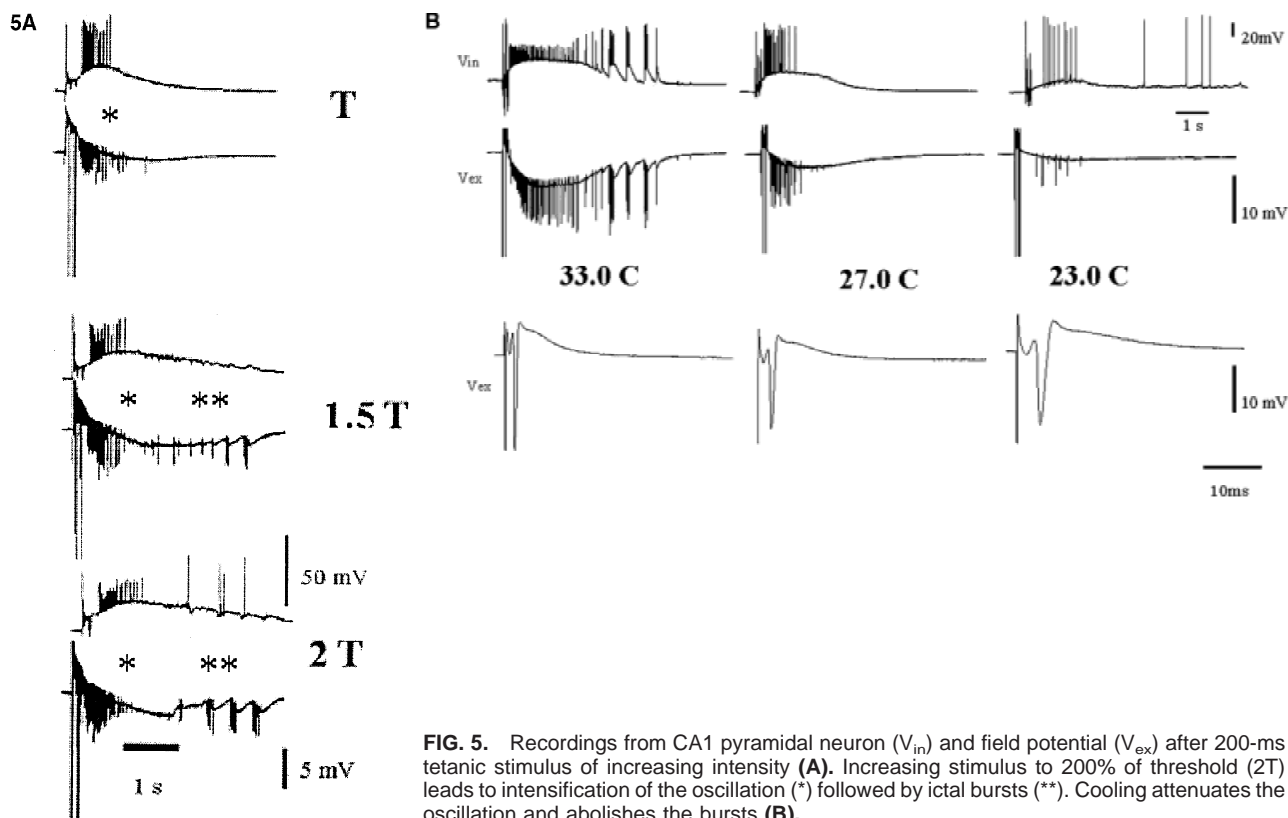
FIG. 5. Recordings from CA1 pyramidal neuron (V_{in}) and field potential (V_{ex}) after 200-ms tetanic stimulus of increasing intensity **(A).** Increasing stimulus to 200% of threshold (2T) leads to intensification of the oscillation (*) followed by ictal bursts (**). Cooling attenuates the oscillation and abolishes the bursts **(B).**

FIG. 6. Field recordings from CA1 before and after exposure to 10 μ*M* BMI, followed by cooling and rewarming the slice. Bicuculline led to multiple population spikes. Cooling changed the shape of the spike, but did not significantly change the amplitude. The change in shape was reversible.

Similar oscillations can be elicited in slices, using low magnesium (12,14; our data, Fig. 2) or high-potassium perfusate (17).

Clinical seizures commonly demonstrate an electroencephalographic pattern of high-frequency (gamma band, >35 Hz) activity as one of the earliest manifestation (18,19). With 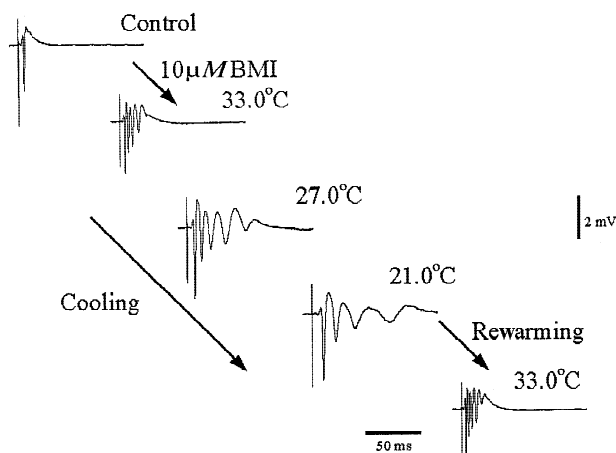routine clinical electroencephalography, this high-frequency EEG activity often is missed, because the skull filters high frequencies, and because muscle artifact may obscure cerebral high-frequency activity. The high-frequency activity is best visualized with depth wire or subdural grid recordings (18). Certain seizures, especially tonic seizures, can present electrodecremental patterns in scalp recordings, with high-frequency activity visible in invasive electrodes (20). When such activity is visible on the scalp, it has been referred to as "generalized paroxysmal fast activity" (21). Whether the fast EEG activity seen at start of clinical seizures is related to the gamma oscillations observed in hippocampal slices remains uncertain.

In laboratory models, gamma oscillations are visible in field recordings, reflecting synchrony of neuronal populations. The synchrony associated with these oscillations has been said to depend on both synaptic and nonsynaptic mechanisms, including alterations in extracellular volume, osmotic conditions, synaptic activity mediated by the metabotropic glutamate receptor, and ephaptic interactions among inhibitory interneurons (12,16,22). Our results provide an example of dissociation between hyperexcitability, represented by multiple population spikes in response to a single stimulus (so-called field "ringing"), and synchrony, reflected by gamma oscillations. A similar type of dissociation was seen in hippocampal slices exposed to furosemide (16).

Effects of cooling on hippocampal slices

Several studies have documented the effect of cooling on unit and field potentials in hippocampal slices (23,24). Moderate cooling (to 27°C) increases resting input resistance (23), which will increase voltage for a given synaptic current. When cooling hippocampal slices from 37 to 20°C, a maximal synaptic potential amplitude is seen between 30 and 27°C; below this temperature, the amplitude decreases, and the latency increases (24). Another study found the evoked field-potential amplitude maximal at 20–25°C in rats and 25–30°C in hamsters (25). Most studies have found a biphasic effect of cooling on evoked field amplitudes, with a slight increase in amplitude with cooling to ~30°C, followed by a gradual decrease in amplitude with further cooling. Hill et al. (11) described elimination of the population spike at 22°C. However, their recordings were from the dentate granule cell layer, not CA1, and they cooled the tissue more rapidly than was done in our experiments. In contrast, Shen and Schwarzkroin (24) showed persistent field potentials, even at 20°C, in rabbit hippocampal CA1 recordings. In addition, Gabriel et al. (25) demonstrated an increase in field-potential amplitude to 20°C, and blockage of field potential only <15°C using CA1 recordings from hamsters. Schiff and Somjen (27) found a decrease in population spike amplitude with warming from 29 to 33 or 37°C, suggesting to the authors that pyramidal cells depolarize with decreasing temperature. Intracellular recordings from pyramidal cells confirmed at depolarization occurred with cooling from 30 to 20–25°C (24). Traynelis and Dingledine (17) showed that temperature reduction to 28–30°C abolished spontaneous electrocorticographic ictal activity in CA1 induced by a perfusate potassium concentration of 8.5 mM. The electrical activity observed by Traynelis had a "tonic" oscillation phase followed by a series of "clonic" bursts, bearing a strong resemblance to the oscillation and subsequent bursts elicited in our experiment with high-intensity tetanic stimulation.

In the current study, cooling to 21°C broadened the population spike but did not significantly change its amplitude. We did not observe the reversible disappearance of synaptic potential reported by Tanimoto and Okada (26) at 22°C. Like others (24), we found it possible to elicit a population spike at temperatures near 21°C, but with increased response latency. We also found no significant effect of cooling on the amplitude or number of multiple population spikes induced by a GABA$_A$ antagonist.

Differences in experimental design and animal models likely account for these somewhat disparate findings, potentially including variations in duration and rapidity of cooling, use of submerged or interface slices, composition of the perfusate, and animal species. Rate of cooling also may be a key variable, because cooling >20 min in our experiments never blocked single evoked population spikes, in distinction to experiments with rapid slice cooling with a Peltier electrical device (11).

Cooling blocks posttetanic oscillation and clonic bursts

Several mechanisms have been offered to explain the anticonvulsant effect of cortical cooling (11,17,29,30) including reduction of transmitter release, alteration of activation–inactivation kinetics of voltage-gated ion channels, mitigation of effects of hypoxia, and a slowing of catabolic processes. However, the mechanisms by which cooling consistently blocked posttetanic oscillations in our experiments are unknown. The posttetanic gamma oscillations blocked by cooling are mediated by GABAergic depolarizations among interneurons in CA1. Although it is possible that cooling selectively inhibits GABAergic transmission in this neuronal population, we did not conduct any experiments on the effect of cooling on GABAergic transmission *per se.* Our findings support a specific effect on network synchrony, rather than any specific effect on synaptic transmission.

Cooling in epilepsy

Studies in patients and animals have demonstrated the utility of cooling in halting seizures. Systemic cooling to <27°C protected against audiogenic seizures in genetically susceptible mice (2). Cooling a penicillin focus substantially reduced penicillin-induced spiking (31,32). In rats, systemic hypothermia to 23°C almost eliminated epileptiform activity induced by parenteral kainic acid (33). Systemic hypothermia protected neocortical tissue in the flurothyl rat model of status epilepticus (34). Vastola et al. (1) reported halting status epilepticus in cats by systemic cooling to 32°C and found systemic hypothermia useful in treating six patients with status epilepticus refractory to medical treatments. Ommaya and Baldwin (5) described a disruption of status epilepticus in one patient and suppression of epileptic activity in six other patients after direct cooling of severely epileptic brain. Sourek and Travnicek (7) showed that some of a group of 23 patients with epilepsy benefited from forced-air cooling and ice applied via burr holes, supplemented with antiepileptic drugs. More recently, intraoperative application of cold Ringer's solution was found to be useful in aborting an induced seizure during cortical mapping (10). Most recently, Yang and Rothman (36) demonstrated that focal cooling of neocortex exposed to 4-AP significantly reduced seizure duration as measured by EEG. Their study raised the possibility of focal cooling triggered by seizure onset as a long-term treatment strategy.

CONCLUSIONS

Our results reaffirm the ability of cooling to reduce epileptiform activity *in vitro.* Cooling to 21°C causes a

reversible block in the network synchrony required to generate gamma oscillations, with preservation of synaptic transmission. As the precise role of gamma oscillations in normal hippocampal function is unknown, it remains to be determined whether cooling would be associated with transient loss of normal function. A moderate level of cooling appears to disrupt GABAergic inhibitory circuits involved in synchronization of epileptiform bursting (35). Such a dissociation between preserved synaptic transmission and disrupted synchrony gives support to the pursuit of cooling as a potential therapy for seizures.

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