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Frequency-dependent inhibition of neuronal activity by topiramate in rat hippocampal slices

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1 Topiramate is a structurally novel anticonvulsant which was recently approved for adjunctive therapy in partial and secondarily generalized seizures. The present study was aimed at elucidating the mechanisms underlying the anticonvulsant efficacy of topiramate using intra- and extracellular recording techniques in the *in vitro* hippocampal slices.

2 When stimuli were delivered every 20 s, topiramate had no measurable effect on both field excitatory postsynaptic potentials (fEPSPs) and population spikes (PSs). However, increasing the stimulation frequency from 0.05–0.2 Hz, topiramate significantly decreased the slope of fEPSP and the amplitude of PS in a concentration-dependent manner. The amplitude of presynaptic fiber volley was also reduced.

3 Topiramate did not affect the magnitude of paired-pulse inhibition and monosynaptically evoked inhibitory postsynaptic potentials (IPSPs).

4 Sustained repetitive firing was elicited by injection of long duration (500 ms) depolarizing current pulses (500–800 pA). Superfusion with topiramate significantly reduced the number of action potentials evoked by a given current pulse.

5 After blockade of GABA receptors by bicuculline, burst firing which consisted of a train of several spikes riding on a large depolarizing wave termed paroxysmal depolarizing shift (PDS) was recorded. Application of topiramate reduced the duration of PDS and later spikes with less effect on the initial action potential.

6 These results suggest that frequency-dependent inhibition of neuronal activity due to blockade of Na^+ channels may account largely for the anticonvulsant efficacy of topiramate.

Keywords: Topiramate; anticonvulsant; synaptic transmission; sodium channel; hippocampus

Introduction

Topiramate, a structurally novel anticonvulsant, was recently approved for adjunctive therapy for partial and secondarily generalized seizures in highly refractory patients (Ben-Menachem *et al*., 1996; Faught *et al*., 1996; Tassinari *et al*., 1996). Previous studies of animal seizure models have shown that topiramate is able to inhibit maximal electroshock-induced seizures in rats and mice (Shank, 1995), sound-induced seizures in DBA/2 mice (Nakamura *et al*., 1994), stroke-induced (Edmonds, *et al*., 1996) and kindled seizures (Wauquier & Zhou, 1996). However, it is not effective in blocking seizures induced by pentylenetetrazol, picrotoxin or bicuculline. It is suggested that topiramate exerts its anticonvulsant effect primarily by blocking the spread of seizures, rather than by elevating the seizure threshold (Shank, 1995).

Multiple mechanisms have been proposed to explain the effect of topiramate, however, the relevance of these actions to the antiepileptic efficacy remained unclear. Electrophysiological studies have shown that topiramate exerts a direct membrane action to reduce neuronal excitability. In cultured hippocampal neurons, topiramate reduced the duration of spontaneous epileptiform bursts and limited repetitive firing of Na^+-dependent action potentials elicited by a depolarizing current pulse (Coulter *et al*., 1993). These effects were generally credited to an ability of this drug to act as state-dependent Na^+ channel blocker (Rogawski & Porter, 1990).

The alternative hypothesis involved an enhancement of γ-aminobutyric acid (GABA)-mediated responses. In cultured cerebellar granule cells, topiramate increased GABA-induced Cl^- fluxes across the membrane (White *et al*., 1997). However, previous ligand-binding studies revealed no interaction between topiramate and GABA-binding sites or benzodiazepine-binding sites on $GABA_A$ receptors (Shank *et al*., 1994). It is possible that topiramate potentiates GABA-mediated responses *via* interaction with a novel modulatory site on some $GABA_A$ receptor subtypes.

Non-N-methyl-D-aspartate (non-NMDA) subtype of glutamate receptors are involved in the generation and expression of some epileptic seizures and antagonists of non-NMDA receptors were known to possess anticonvulsant activity (Chapman *et al*., 1991; Yamaguchi, *et al*., 1993). In cultured hippocampal neurons, topiramate has been shown to inhibit kainate-induced inward currents (Severt *et al*., 1995).

Electrophysiological data regarding the mechanism of action for topiramate so far were limited, which appeared as an abstract form and obtained from cultured neurons (Coulter *et al*., 1993). In the present study, we examined the effect of this drug on the neuronal activity in hippocampal slices, a more physiologically relevant preparation. We found that topiramate inhibits neuronal activity in a frequency-dependent fashion without affecting normal synaptic transmission. This activity-dependent mode of action endows topiramate a characteristic that may selectively suppress abberant excitability while sparing normal neuronal activity.

Methods

Male Sprague-Dawley rats of 4–6-weeks-old were decapitated and the brains rapidly removed from the skull. Coronal slices of 400–450 μM thick were cut and the appropriate slices were placed in a beaker of artificial cerebrospinal fluid (ACSF). The

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ACSF was bubbled continuously with 95% O_2-5% CO_2 to maintain the proper pH (7.3–7.5). The composition of the ACSF solution was (in mM): NaCl 117, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaHCO_3$ 25, NaH_2PO_4 1.2 and glucose 11.

The slices were kept at room temperature for at least 1 h before recording. A single slice was then transferred to the recording chamber where it was held submerged between two nylon nets and maintained at 32 ± 1°C. The chamber consisted of a circular well of low volume (1–1.5 ml) and was constantly perfused at a rate of 3–4 ml min^{-1}.

Extracellular recordings of field excitatory postsynaptic potentials (fEPSPs) and population spikes (PSs) were obtained from stratum radiatum and stratum pyramidale respectively using microelectrodes filled with 3 M NaCl (3–8 MΩ). A bipolar stimulating electrode (SNE-200X, Kopf Ins., Tujunga, CA, U.S.A.) was placed in stratum radiatum for stimulation of Schaffer collateral/commissural pathway. The stimulus duration was 150 μs and the stimulus intensity was adjusted individually for each experiment to produce fEPSP and population spikes which were 40–50% of the maximal responses that could be evoked. Experimental treatments were not initiated until the responses had been stable for at least 20 min. The strength of synaptic transmission was quantified by measuring the initial slope of the fEPSP and the amplitude of population spikes. The fEPSP slope were measured by linear regression of its initial rising phase usually during the first 0.4–0.6 ms after their onset. Onset was taken after the afferent volley. Population spike amplitudes were measured as the difference between negative peak and the average value of the following positive peak.

Intracellular recordings were made with conventional intracellular recording techniques. Microelectrodes were pulled from microfiber-filled 1.0 mm capillary tubing on a Brown-Flaming electrode puller (Sutter Instruments, Novato, CA, U.S.A.). The electrodes were filled with 4 M potassium acetate with resistance ranging from 80–130 MΩ. Membrane input resistance was measured by passing a current of 100 ms duration and recording the resultant electrotonic potentials. For data acquisition and analysis, pClamp 6.0 (Axon Instruments, Foster City, CA, U.S.A.) running on PC486 computer was used. All data were expressed as mean $\pm$ s.e.m. Statistical analysis was performed using the Student's *t*-test and a *P* value of less than 0.05 was considered to be statistically significant. Topiramate was kindly provided by the Janssen-Cilag company (New Brunswick, NJ, U.S.A.). CNQX and D-APV were purchased from Research Biochemicals International (Natick, MA, U.S.A.) and bicuculline methiodide from Sigma Chemicals (St. Louis, MO, U.S.A.).

Results

Effect of topiramate on the fEPSP and PS

When stimuli were delivered every 20 s, topiramate (10–100 μM) had no measurable effect on both fEPSP and PS (Figure 1). After an application period of 50 min, the slope of fEPSP and the amplitude of PS were $98 \pm 6\%$ ($n=6$) and $103 \pm 4\%$ ($n=10$) of baseline respectively. However, as shown in Figure 2, topiramate slowly and significantly suppressed the population spikes when the frequency of stimulus was increased from 1 pulse per 20 s to 1 pulse per 5 s. The effect of topiramate was concentration-dependent with EC_{50} of 9 μM and maximal inhibition of $52 \pm 6\%$ (Figure 2A). Topiramate-induced inhibition was not reversible during washout up to 2 h ($n=4$, data not shown). Similar phenomenon of frequency-dependent inhibition was observed in fEPSP (Figure 3). On average, fEPSP slope was reduced by $44 \pm 8\%$ ($n=6$) in the

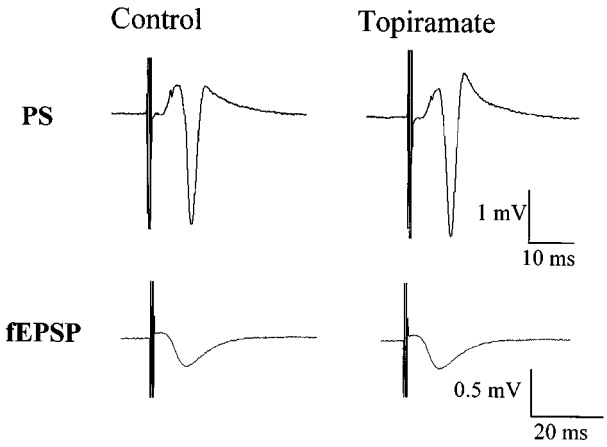

Figure 1 Topiramate has no effect on both PS and fEPSP at the stimulation frequency of 0.05 Hz. PSs and fEPSPs were elicited by electrical stimulation of the Schaffer collaterals every 20 s in control solution and during the application of topiramate (100 μM). Each trace represents the average of 15 responses.

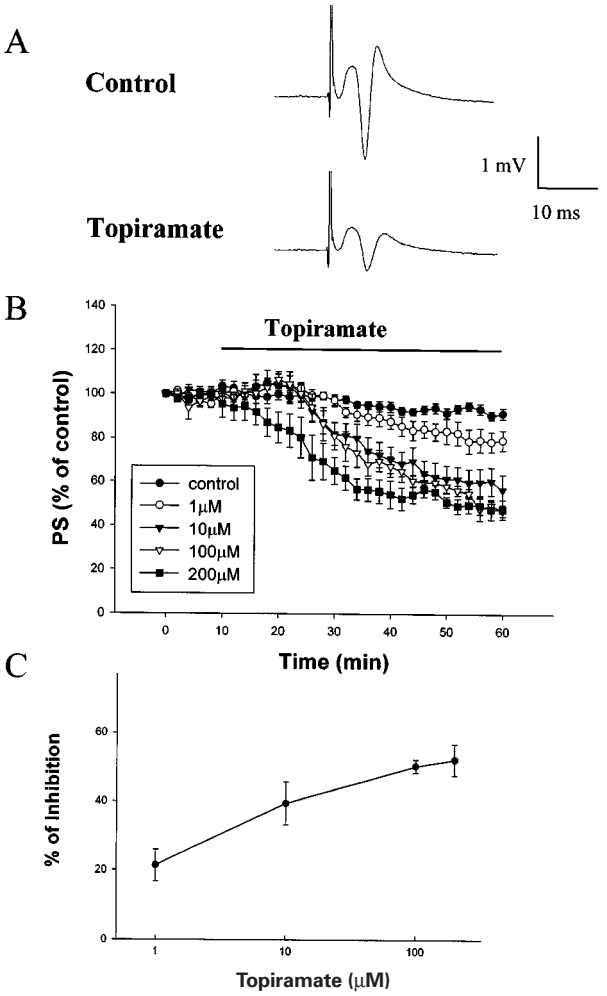

Figure 2 Topiramate depresses the PS when the stimulation frequency is increased to 0.2 Hz. (A) Typical PSs recorded under control condition and 50 min in the presence of 100 μM topiramate. (B) Time course of the action of topiramate on the PS. (C) Concentration-dependent depression of the PS by topiramate.

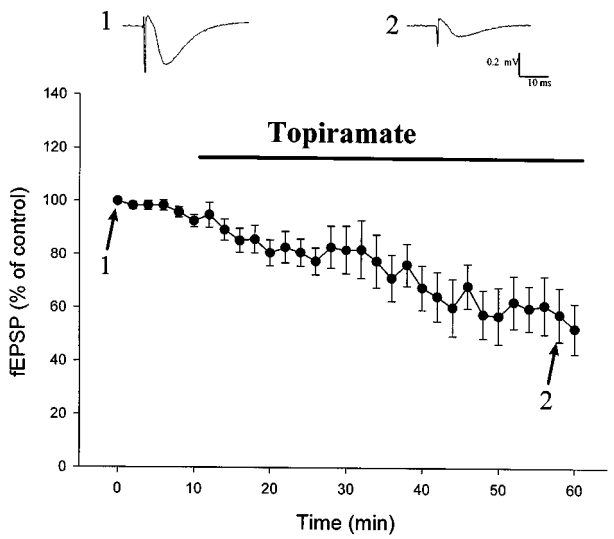

Figure 3 Inhibitory action of topiramate on the fEPSP. fEPSPs were elicited by electrical stimulation of Schaffer collaterals every 5 s. Bar denotes the period of application of topiramate (50 μM).

presence of 50 μM topiramate. Again, the effect of topiramate was irreversible 60 min after washout of the drug.

Effect of topiramate on the presynaptic fiber volley

We investigated the effect of topiramate on the presynaptic fiber volley which represents the compound action potential generated in presynaptic axons. To quantify this effect, we isolated the fiber volley by recording the population spikes in the presence of 6-cyano-7-notroquinoxaline-2,3-dione (CNQX, 10 μM), D-2-amino-5-phosphonovalerate (APV, 20 μM) and bicuculline (Bic, 20 μM) to block postsynaptic potentials and by placing the stimulating electrode closer than usual to the recording electrode (Figure 4A). The isolated fiber volley was blocked by tetrodotoxin (TTX, 1 μM), confirming that this extracellular potential reflects synchronized action potentials in presynaptic axons arising from CA3 neurons (Figure 4B). With a stimulus frequency of 0.2 Hz, application of topiramate (100 μM) slowly reduced the amplitude of fiber volley by $54 \pm 8\%$ ($n = 6$) (Figure 4C). Furthermore, when examined carefully, it can been seen from Figures 2B and 4C that the reduction of presynaptic fiber volley preceded the inhibition of post-synaptic population spikes suggesting an involvement of presynaptic site of action.

Paired-pulse facilitation

We further examined whether topiramate-induced inhibition of population spikes involves a presynaptic mechanism that could be detected with the paradigm of paired-pulse facilitation (PPF). This stimulus pattern, which has been used to differentiate the site of induction and expression of long-term potentiation (Manabe *et al*., 1993; Schulz *et al*., 1994), induces for a short time an increase in transmitter release resulting from the residual presynaptic free Ca^{2+} levels. A pair of synaptic responses was elicited with an interstimulus interval of 50–60 msec, and the ratio of the second response to the first one was monitored continuously during the experiment. Figure 5 shows that the reduction of fEPSP slope induced by topiramate was not accompanied by the change of

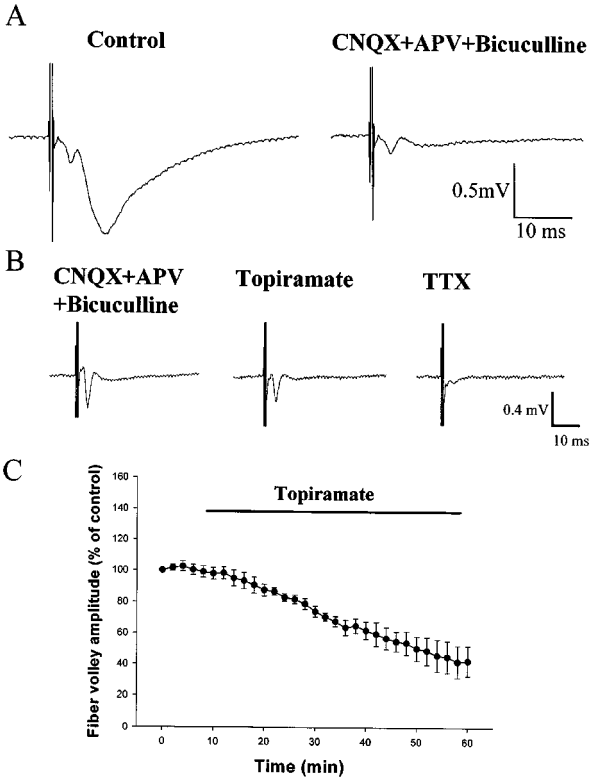

Figure 4 Topiramate depresses the amplitude of pharmacologically isolated fiber volley. (A) Pharmacological isolation of presynaptic fiber volley. Afferent stimulation evoked a fiber volley followed by the postsynaptic potential which was blocked by CNQX (10 μM) + APV (20 μM) + Bic (20 μM). (B) This fiber volley, elicited every 5 s and in the presence of CNQX + APV + Bic, was sensitive to TTX (1 μM) and was depressed by topiramate. (C) Time course of the action of topiramate on the presynaptic fiber volley.

PPF. The ratio of PPF was 1.22 ± 0.07 before and 1.20 ± 0.08 ($n = 8$) during the application of topiramate.

Paired-pulse inhibition

Paired-pulse modulation in the hippocampal CA1 region has been well characterized (Creager *et al*., 1980; Dunwiddie *et al*., 1980). Facilitation is most easily seen when the interstimulus interval is 50–60 ms. Conversely, inhibition is demonstrated at interstimulus intervals less than 40 ms, which correspond to the the time course of $GABA_A$ receptor-mediated fast inhibitory potentials (IPSPs). Paired-pulse inhibition is therefore thought to be largely caused by the activation of $GABA_A$ receptors. It has been suggested that topiramate exerts its anticonvulsant activity by potentiating $GABA_A$ receptor-mediated responses (White *et al*., 1997). We tested this hypothesis by investigating the effect of topiramate on the paired-pulse inhibition. Synaptic responses to a pair of stimuli were recorded with interstimulus interval of 15 ms. The stimulus strength was adjusted in each experiment so that the first population spike was always greater in amplitude than the second one. Figure 6A is a summary of eight experiments showing that topiramate did not affect the magnitude of paired-pulse inhibition. The ratio of the second response (P2) to the first one (P1) was 0.65 ± 0.09 before and 0.68 ± 0.09 ($n = 8$) 50 min in the presence of topiramate (100 μM).

We further determined whether topiramate affects $GABA_A$ receptor-mediated IPSP. Monosynaptic IPSPs were evoked by focal stimulation in the presence of glutamate receptor

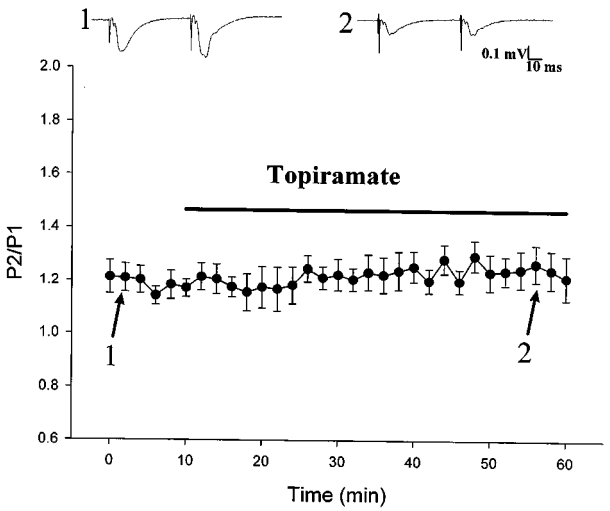

Figure 5 The ratio of paired-pulse facilitation is not changed by topiramate-induced inhibition. Time course of the action of topiramate (100 μM) on the ratio of PPF. fEPSPs were evoked by paired stimuli (60 ms interval) every 5 s.

antagonists, CNQX (10 μM) and D-APV (20 μM). Depolarization of the membrane potential increased the amplitude of IPSP whereas hyperpolarization of the membrane potential decreased the amplitude of IPSP. In six neurons, IPSP reversed polarity at -68 ± 2 mV (data not shown) corresponding to the reversal potential for chloride ions. Figure 6B is a summary of six experiments showing that topiramate had no effect on the IPSP. The amplitude of IPSP was $94 \pm 6\%$ ($n=6$) of control in the presence of topiramate.

Effect of topiramate on repetitive firing of action potentials

Two distinct firing patterns were observed in response to 500-ms depolarizing current pulse. Of 20 neurons tested, eight cells showed profound accommodation of repetitive spike firing during depolarizing current injection (Figure 7B). Accommodation was defined as the slowing of action potential firing during the initial (200 ms) segment of the depolarizing current injection, which curtailed with continued depolarization. The remaining 12 cells showed little, if any, accommodation that could sustain repetitive action potential firing throughout the

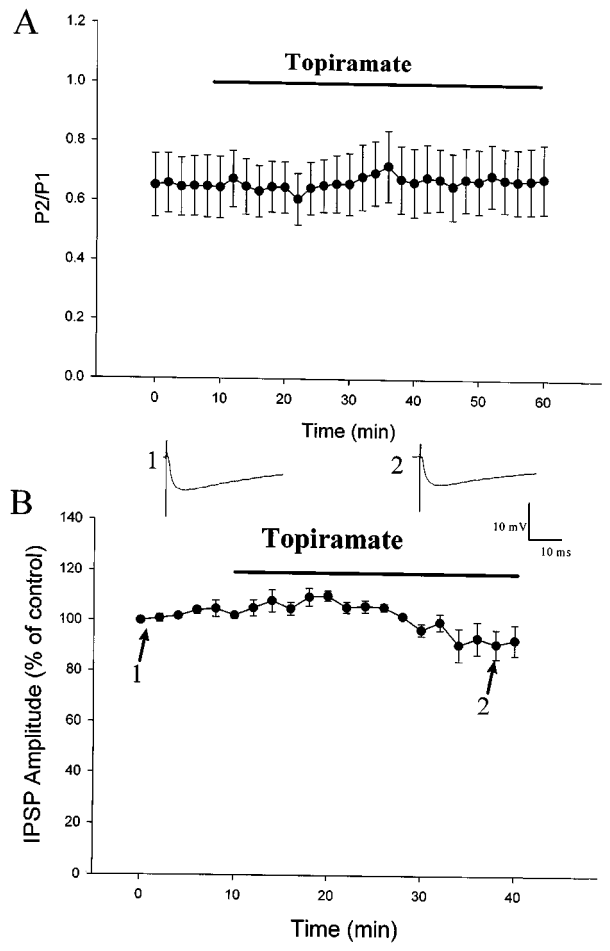

Figure 6 Topiramate does not affect paired-pulse inhibition and monosynaptically evoked IPSP. (A) Time course of the action of topiramate (100 μM) on the paired-pulse inhibition. (B) Time course of the action of topiramate (100 μM) on the monosynaptically evoked IPSP. Inset shows typical IPSPs recorded under control and 25 min in the presence of topiramate (100 μM). The cell was held at -55 mV. The resting membrane potential of this cell was -72 mV. Monosynaptical IPSPs were elicited in the presence of glutamate receptor antagonists (10 μM CNQX + 20 μM APV).

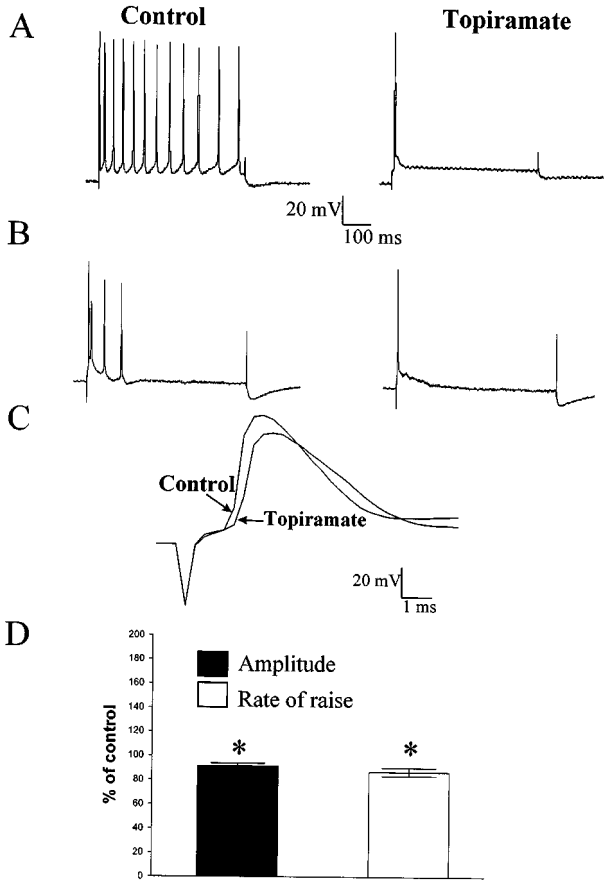

Figure 7 Topiramate limits sustained repetitive firing. (A) Typical voltage responses of a non-accommodating neuron on injection of a current pulse (500 pA, 500 ms) in control and during the application of topiramate (20 μM). The resting membrane potential was -68 mV. (B) Typical voltage responses of an accommodating neuron on injection of a current pulse (800 pA, 500 ms) in control and during the application of topiramate (20 μM). The resting membrane potential was -66 mV. (C) Both amplitude and rate of rise of the initial action potential were attenuated by topiramate. The traces in (B) and (C) were taken from the same cell. (D) Graphic analysis of the effect of topiramate on the amplitude and rate of rise of the initial action potential.**$P<0.01$ *vs* control.

period of depolarizing current injection (Figure 7A). As shown in Figure 7, superfusion with topiramate (20 μM) markedly reduced the total number of action potential evoked by a depolarizing current pulse in both accommodating and non-accommodating cells.

In addition to its effect on repetitive firing, topiramate altered the properties of the individual action potential. Figure 7C illustrates that topiramate significantly reduced the amplitude and rate-of-rise of the first spike. The amplitude and rate of rise were $91 \pm 2\%$ ($n=8$, $P<0.01$) and $86 \pm 2\%$ ($n=8$, $P<0.01$) of control respectively (Figure 7D).

Antiepileptic effect of topiramate

After blockade of γ-aminobutyric acid$_A$ ($GABA_A$) receptors by bicuculline (20 μM), epileptiform activity manifested as three to four spikes riding on a large depolarizing wave termed paroxysmal depolarizing shift (PDS) could be induced in the hippocampal CA1 neurones. Figure 8 shows that application of topiramate (50 μM) reduced the duration and the later spikes riding on the PDS. As shown in Figure 8, the synaptic stimulation was preceded by a hyperpolarizing current pulse (100 pA, 100 ms) passed through the recording electrode to monitor the neuronal input resistance. Neither resting membrane potential nor input resistance was altered by topiramate.

Discussion

The major findings of this study are: (1) topiramate reduced the slope of fEPSP and the amplitude of PS in a frequency- and concentration-dependent manner; (2) topiramate reduced the amplitude of pharmacologically isolated presynaptic fiber volley without affecting the ratio of paired-pulse facilitation; (3) topiramate affect neither paired-pulse inhibition nor GABAergic-mediated IPSP; (4) topiramate reduced the total number of action potentials evoked by a depolarizing current pulse; and (5) topiramate suppressed the the bicuculline-induced PDS.

In general, three major cellular actions have been proposed to contribute to the anticonvulsant efficacy of topiramate: blockade of Na^+ channels, antagonism of non-NMDA receptors and enhancement of GABA-mediated responses. In the present study, we found that topiramate at concentrations up to 100 μM had no significant effect on both fEPSP and PS at lower stimulus frequency (1 pulse per 20 s). These results indicate that at therapeutically relevant concentrations topiramate did not act on non-NMDA receptors because glutamate is the principal neurotransmitter in Schaffer collateral-CA1 synapses (Collingridge *et al*., 1983; Collingridge & Lester, 1989) which could be blocked by CNQX, a non-NMDA receptor antagonist (Andreasen *et al*., 1989). These results are in contrast with a previous report showing that kainate-induced inward currents in cultured hippocampal neurons were inhibited by topiramate (Severt *et al*., 1995). The lack of effect in the present investigation may reflect the different preparations employed (cultured neurons *vs* slice preparation). However, increasing the frequency of stimulation from 1 pulse per 20 s to 1 pulse per 5 s enables the topiramate-induced inhibition of fEPSP and PS. By the use of TTX, we have identified the negative deflection preceding the population spike as the presynaptic fiber spike, which represents compound action potentials of the Schaffer collaterals. The presynaptic fiber spike was depressed by topiramate at the stimulation frequency of 0.2 Hz but not at 0.05 Hz. The frequency-dependent inhibition of fEPSP, PS and presynaptic fiber spike suggests that topiramate may block Na^+ channels thereby stabilizing presynaptic membranes and decreasing the release of transmitter.

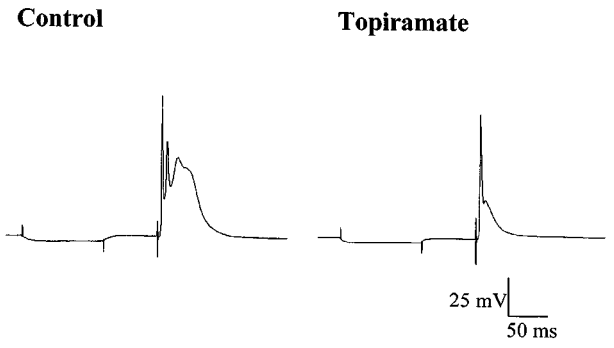

Figure 8 Effect of topiramate on the paroxysmal depolarizing shift induced by bicuculline. In the presence of bicuculline (20 μM), afferent stimulation evoked a PDS which was depressed by topiramate (50 μM). The synaptic stimulation was preceded by a transient hyperpolarizing current pulse (100 pA, 100 ms) passed through the recording electrode to monitor the input resistance. The resting membrane potential and input resistance were -65 mV and 36 MΩ respectively.

In the present study, we found that topiramate reduced the total number of action potentials evoked by a depolarizing current pulse in both accommodating and non-accommodating cells. The spike amplitude and rate-of-rise which were often used as an indirect measure of the maximal Na^+ conductance were depressed in the presence of topiramate. In addition, topiramate reduced the duration and the spikes riding on the paroxysmal depolarizing shift. These characteristics could be credited to a state-dependent Na^+ channel blocking mechanism (Rogawski & Porter, 1990) and were shared by anticonvulsant drugs such as phenytoin, carbamazepine and lamotrigine (Willow *et al*., 1985; Leach *et al*., 1986; Backus *et al*., 1991). However, unlike topiramate, these drugs act by more than one mechanism and inhibit synaptic responses at a low stimulation frequency (1 pulse per 20 s), an effect which is likely due to inhibition on the Ca^{2+} channels (Wang *et al*., 1996; Stefani *et al*., 1996; Cheng *et al*., 1997). In this respect, topiramate is expected to provide a more selective therapy with fewer adverse effects, although the question of whether an absolute selectivity of a drug is desirable in seizure therapy that involves complex adaptive changes is still in doubt (Loscher, 1998).

We have also tested a possible presynaptic contribution on the topiramate-induced inhibition by using the paired-pulse facilitation paradigm. PPF, a phenomenon generally accepted to be presynaptic (Zucker, 1989), is altered by manipulations that change intraterminal Ca^{2+} concentrations and the probability of transmitter release (Manabe *et al*., 1993; Schulz *et al*., 1994). The lack of change in PPF suggests that the inhibition induced by topiramate does not interfere with the presynaptic mechanisms involved in this kind of facilitation. It has been reported that recruiting additional afferent fibers by increasing the stimulus intensity (Manabe *et al*., 1993) or increment in presynaptic axon excitability by application of taurine (Galarreta *et al*., 1996) resulted in synaptic potentiation without altering PPF. Thus, a simple explanation for topiramate-induced inhibition is a reduction of afferent fibers been stimulated or axon excitability.

Potentiation of GABA-mediated responses is an important mechanism of anticonvulsant action (Granger *et al*., 1995;

Meldrum, 1995; Olsen & Avoli, 1997). It has been shown that topiramate increased GABA-induced Cl^- flux across the membranes of cultured cerebellar granule cells. Topiramate also enhanced GABA-evoked whole cell Cl^- currents in mouse cerebral cortical neurons in culture (White *et al*., 1997). On the other hand, in ligand binding studies topiramate did not interact with GABA binding sites or benzodiazepine binding sites on $GABA_A$ receptors (Shank *et al*., 1994). In the present study, neither paired-pulse inhibition nor GABAergic IPSPs were affected suggesting that the effect of topiramate on the GABAergic system is not a significant factor in its anticonvulsant activity. The discrepancy between our and some previous results in the effect of topiramate on inhibitory synaptic transmission could be attributed to the different experimental preparations employed (slice preparation as opposed to neuronal culture).

In conclusion, the activity-dependent inhibition of fEPSP, PS and presynaptic fiber volley by topiramate coupled with the limitation of repetitive firing of action potentials suggests that Na^+ channels blockade may be the underlying mechanism. Consistent with these results, preclinical animal tests have shown that topiramate is highly effective against maximal electroshock seizure test (Shank, 1995), predictive of anticonvulsant efficacy against partial and generalized tonic-clonic seizures in humans (Loscher, 1998). The activity-dependent mode of action endows topiramate a characteristic that it may selectively suppress abberant excitability, thus blocking the generation and spread of epileptic seizures while sparing normal neuronal activity.

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References

ANDREASEN, M., LAMBERT, J.D.C. & JENSEN, M.S. (1989). Effects of new non-N-methyl-D-aspartate antagonists on synaptic transmission in the in vitro rat hippocampus. *J. Physiol.,* **414,** 317–336.

BACKUS, K.H., PFLIMLIN, P. & TRUBE, G. (1991). Action of diazepam on the voltage-dependent Na^+ current. Comparison with the effects of phenytoin, carbamazepine, lidocaine and flumazenil. *Brain Res.,* **548,** 41–49.

BEN-MENACHEM, E., HENRIKSEN, O., DAM, M., MIKKELSEN, M., SCHMIDT, D., REID, S., REIFE, R., KRAMER, L., PLEDGER, G. & KARIM, R. (1996). Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia,* **37,** 539–543.

CHAPMAN, A.G., SMITH, S.E. & MELDRUM, B.S. (1991). The anticonvulsant effect of the non-NMDA antagonists, NBQX and GYKI 52466, in mice. *Epilepsy Res.,* **9,** 92–96.

CHENG, L.L., WANG, S.J., TSAI, J.J. & GEAN, P.W. (1997). Effects of phenytoin on the amygdala neurons in vitro. *Pharmacology,* **55,** 228–234.

COLLINGRIDGE, G.L., KEHL, S.J. & MCLENNAN, H. (1983). Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. *J. Physiol.,* **334,** 33–46.

COLLINGRIDGE, G.L. & LESTER, R.A.J. (1989). Excitatory amino acid receptors in the vertebrate central nervous system. *Pharmacol. Rev.,* **40,** 143–210.

COULTER, D.A., SOMBATI, S. & DELORENZO, R.J. (1993). Selective effects of topiramate on sustained repetitive firing and spontaneous bursting in cultured hippocampal neurons. *Epilepsia,* **34,** S123.

CREAGER, R., DUNWIDDIE, T. & LYNCH, G. (1980). Paired-pulse and frequency facilitation in the CA1 region of the in vitro rat hippocampus. *J. Physiol.,* **299,** 409–424.

DUNWIDDIE, T., MUELLER, A., PALMER, M., STEWART, J. & HOFFER, B. (1980). Electrophysiological interactions of enkephalins with neuronal circuitry in the rat hippocampus. I. Effects on pyramidal cell activity. *Brain Res.,* **184,** 311–330.

EDMONDS JR, H.L., JIANG, Y.D., ZHANG, P.Y. & SHANK, R.P. (1996). Anticonvulsant activity of topiramate and phenytoin in a rat model of ischemia-induced epilepsy. *Life Sciences,* **59,** 127–131.

FAUGHT, E., WILDER, B.J., RAMSAY, R.E., REIFE, R.A., KRAMER, L.D., PLEDGER, G.W. & KARIM, R.M. (1996). Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosage (and the T.Y.S. group). *Neurology,* **46,** 1684–1690.

GALARRETA, M., BUSTAMANTE, J., MARTIN DEL RIO, R. & SOLIS, J.M. (1996). Taurine induces a long-lasting increase of synaptic efficacy and axon excitability in the hippocampus. *J. Neurosci.,* **16,** 92–102.

GRANGER, P., BITON, B., FAURE, C., VIGE, X., DEPOORTERE, H., GRAHAM, D., LANGER, S.Z., SCATTON, B. & AVENET, P. (1995). Modulation of the γ-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin. *J. Pharmacol. Exp. Ther.,* **47,** 1189–1196.

LEACH, M.J., MARDEN, C.M. & MILLER, A.A. (1986). Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. *Epilepsia,* **27,** 490–497.

LOSCHER, W. (1998). New visions in the pharmacology of anticonvulsion. *Eur. J. Pharmac.,* **342,** 1–13.

MANABE, T., WYLLIE, D.J.I. & NICOLL, R.A. (1993). Modulation of synaptic transmission and long-term potentiation: effects on paired-pulse facilitation and EPSP variance in the CA1 region of the hippocampus. *J. Neurophysiol.,* **70,** 1451–1459.

MELDRUM, B.S. (1995). Neurotransmission in epilepsy. *Epilepsia,* **36,** S30–S35.

NAKAMURA, J., TAMURA, S., KANDA, T., ISHII, A., ISSHIHARA, K., SERIKAWA, T., YAMADA, J. & SASA, M. (1994). Inhibition by topiramate of seizures in spontaneously epileptic rats and DBA/2 mice. *Eur. J. Pharmacol.,* **254,** 83–89.

OLSEN, R.W. & AVOLI, M. (1997). GABA and epileptogenesis. *Epilepsia,* **38,** 399–407.

ROGAWSKI, M.A. & PORTER, R.J. (1990). Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacol. Rev.,* **42,** 223–286.

SCHULZ, P.E., COOK, E.P. & JOHNSTON, D. (1994). Changes in paired-pulse facilitation suggest presynaptic involvement in long-term potentiation. *J. Neurosci.,* **14,** 5325–5337.

SEVERT, L., COULTER, D.A., SOMBATI, S. & DELORENZO, R.J. (1995). Topiramate selectively blocks kainate currents in cultured hippocampal neurons. *Epilepsia,* **36,** S38.

SHANK, R.P. (1995). Preclinical profile of topiramate, a novel anticonvulsant. *Adv. AED. Ther.,* **1,** 1–6.

SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O. & MARYANOFF, B.E. (1994). Topiramate: Preclinical evaluation of a structurally novel anticonvulsant. *Epilepsia,* **35,** 449–460.

STEFANI, A., SPADONI, F., SINISCALCHI, A. & BERNARDI, G. (1996). Lamotrigine inhibits Ca^{++} currents in cortical neurons: functional implications. *Eur. J. Pharmac.,* **307,** 113–116.

TASSINARI, C.A., MICHELUCCI, R., CHAUVEL, P., CHODKIEWICZ, J., SHORVON, S., HENRIKSEN, O., DAM, M., REIFE, R., PLEDGER, G. & KARIM, R. (1996). Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy. *Eplepsia,* **37,** 763–768.

WANG, S.J., HUANG, C.C., HSU, K.S., TSAI, J.J. & GEAN, P.W. (1996). Presynaptic inhibition of excitatory neurotransmission by lamotrigine in the rat amygdalar neurons. *Synapse,* **24,** 248–255.

WAUQUIER, A. & ZHOU, S. (1996). Topiramate: a potent anticonvulsant in the amygdala-kindled rat. *Epilepsy Res.,* **24,** 73–77.

WHITE, H.S., BROWN, S.D., WOODHEAD, J.H., SKEEN, G.A. & WOLF, H.H. (1997). Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. *Epilepsy Res.,* **28,** 167–179.

WILLOW, M., GONOI, T. & CATTERALL, W.A. (1985). Voltage clamp analysis of the inhibitory actions of diphenylhydantoin and carbamazepine on voltage-sensitive sodium channels in neuroblastoma cells. *Mol. Pharmacol.,* **27,** 549–558.

YAMAGUCHI, S., DONEVAN, S.D. & ROGAWSKI, M.A. (1993). Anticonvulsant activity of AMPA/kainate antagonists: Comparison of GYKI 42466 and NBQX in maximal electroshock and chemoconvulsant seizure models. *Epilepsy Res.,* **15,** 179–184.

ZUCKER, R.S. (1989). Short-term synaptic plasticity. *Ann. Rev. Neurosci.,* **12,** 13–31.

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