KCNQ/Kv7 Channel Regulation of Hippocampal Gamma-Frequency Firing in the Absence of Synaptic Transmission

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Piccinin, S., A. D. Randall, and J. T. Brown. KCNQ/Kv7 channel regulation of hippocampal gamma-frequency firing in the absence of synaptic transmission. J Neurophysiol 95: 3105–3112, 2006. First published February 8, 2006; doi:10.1152/jn.01083.2005. Synchronous neuronal firing can be induced in hippocampal slices in the absence of synaptic transmission by lowering extracellular Ca2+ and raising extracellular K+. However, the ionic mechanisms underlying nonsynaptic synchronous firing are not well understood. In this study we have investigated the role of KCNQ/Kv7 channels in regulating this form of nonsynaptic bursting activity. Incubation of rat hippocampal slices in reduced (0.2 mM) [Ca2+]o increased (6.3 mM) [K+]o blocked synaptic transmission, increased neuronal firing and led to the development of spontaneous periodic nonsynaptic epileptiform activity. This activity was recorded extracellularly as large (4.7 ± 1.9 mV) depolarizing envelopes with superimposed high-frequency synchronous population spikes. These intraburst population spikes initially occurred at a high frequency (about 120 Hz), which decayed throughout the burst stabilizing in the gamma-frequency band (30–80 Hz). Further increasing [K+]o resulted in an increase in the interburst frequency without altering the intraburst population spike frequency. Application of retigabine (10 μM), a Kv7 channel modulator, completely abolished the bursts, in an XE-991–sensitive manner. Furthermore, application of the Kv7 channel blockers, linopirdine (10 μM) or XE-991 (10 μM) alone, abolished the gamma frequency, but not the higher-frequency population spike firing observed during low Ca2+/high K+ bursts. These data suggest that Kv7 channels are likely to play a role in the regulation of synchronous population firing activity.

INRODUCTION

The M-current (I_M) is a voltage-sensitive slowly activating and noninactivating K+ conductance. I_M was first described as a current suppressed by muscarinic acetylcholine receptor (mAChR) activation in bullfrog sympathetic ganglia (Brown and Adams 1980), and has since been described in a wide range of mammalian neuronal tissue including hippocampal (Halliwell and Adams 1982; Selyanko and Sim 1998) and cortical neurons (Otto et al. 2002). The channels that mediated I_M are thought to be members of the Kv7 K+ channel family (also known as KCNQ channels) (Wang et al. 1998), consisting of Kv7.1 to Kv7.5 (Robbins 2001). In peripheral sympathetic neurons, M-channels are thought to be composed of heteromeric assemblies of Kv7.2 and Kv7.3 subunits (Wang et al. 1998), whereas in hippocampal neurons, Kv7.5 is also thought to contribute to I_M (Shah et al. 2002).

I_M is critically important for controlling neuronal excitability because it is active at membrane potentials close to the physiological resting potential of many CNS neurons (Brown and Adams 1980; Halliwell and Adams 1982; Storm 1988). For instance, in hippocampal CA1 pyramidal neurons, I_M has been shown to play a role in spike frequency adaptation (Gu et al. 2005; Otto et al. 2002; Peters et al. 2005; Yue and Yaari 2004), medium afterhyperpolarization (Gu et al. 2005; Peters et al. 2005), afterdepolarization (Yue and Yaari 2004), and theta frequency band membrane resonance (Hu et al. 2002; Peters et al. 2005). Furthermore, in the hippocampus, I_M is modulated by the activity of a range of postsynaptic receptors (Marriion 1997), including mAChRs (Halliwell and Adams 1982; Selyanko et al. 2000) and metabotropic glutamate receptors (Charpak et al. 1990). Comparatively little is known, however, about how an intrinsic I_M conductance contributes to the complex interplay of activity that occurs within an active neuronal network.

Synchronization of neural activity within neuronal networks is of fundamental importance to a wide range of brain functions, including cognitive processing and temporal binding (Buzsáki 2002). Furthermore, under pathological conditions such as epilepsy, hyperexcitable synchronized network activity results in seizures (Traube et al. 1999). Typically, network synchronization is thought of in terms of classical chemical synaptic communication, although there is a body of evidence to suggest that nonsynaptic, intrinsic electrical activity contributes to network dynamics (Jefferys 1995). Indeed, spontaneous synchronous bursting activity can be observed in hippocampal slices in vitro under conditions whereby Ca2+-mediated synaptic transmission is abolished (Haas and Jefferys 1984; Jefferys and Haas 1982; Taylor and Dudek 1982; Thuaulet et al. 2002; Xiong and Stringer 2001). Such activity is induced by increasing [K+]o and removing, or significantly reducing, [Ca2+]o, leading to neuronal depolarization and hyperexcitability through both the shift in the potassium equilibrium potential and reduced divalent ion–mediated surface charge screening. However, the ionic conductances that underlie this form of synchronous activity remain obscure. The role of several ionic currents have been shown to play a role in generating and/or modulating low Ca2+ bursting activity, including I_h (Gill et al. 2006), a persistent Na+ current (Bikson et al. 2003b), and G-protein–coupled K+ currents (Xiong and Stringer 2001).

In this study we used pharmacological tools that modulate Kv7 channel function to assess the role of I_M in hippocampal nonsynaptic synchronous bursting activity. Retigabine [N-(2-amino-4-(4-fluorobenzylamino)-phenyl)carbamoyl acid ethyl
ester], an anticonvulsant undergoing clinical development, has been shown to shift the voltage activation curve of Kv7.2/3 heteromers such that the channels were opened at more hyperpolarized membrane potentials (Main et al. 2000; Rundfeldt and Netzer 2000; Tatulian and Brown 2003; Tatulian et al. 2001; Wickenden et al. 2000). In a native CNS preparation such as the hippocampal slice, this compound would potentially act as a Kv7 channel opener (Gu et al. 2005). We sought to establish whether retigabine could downregulate nonsynaptic bursting activity. To directly determine whether Kv7 channels regulate the pattern of bursting activity under normal conditions, we used the Kv7 channel blockers linopirdine [3,3-bis(4-pyridinylmethyl)-1-phenylindolin-2-one] and XE991 [10,10-bis(4-pyridinylmethyl)-9(10H)-anthracene].

METHODS

Preparation of hippocampal slices

Male hooded Lister rats were killed by overdose of isoflurane followed by cervical dislocation, in accordance with UK Home Office regulations. The brains were rapidly removed and mounted on a steel plate; 400-μm-thick sections of whole brain were made using a vibroslicer (Leica Microsystems, Milton Keynes, UK). Sectioning was performed in a cold (about 4°C) sucrose-based slicing solution consisting of (in mM): sucrose, 189; d-glucose, 10; NaHCO3, 26; KCl, 3; MgCl2, 5; CaCl2, 0.1; and NaH2PO4, 1.25. The solution was continuously bubbled with carbogen (95% O2-5% CO2). After slicing the hippocampus was dissected free and transferred to an interface recording chamber continuously perfused with warmed (32°C) carbogen-bubbled NaCl-based artificial cerebrospinal fluid (aCSF) containing (in mM): NaCl, 124; KCl, 3; NaHCO3, 26; CaCl2, 2; NaH2PO4, 1.25; MgSO4, 1; and d-glucose, 10.

Extracellular recordings and analysis

After an equilibration period of ≈1 h, extracellular field potential recordings were made from stratum pyramidale in area CA1 using glass micropipettes (2–4 MΩ) back-filled with aCSF. Correct positioning of the recording electrode was confirmed by stimulating the Schaffer collateral pathway to elicit a synaptic response. To generate nonsynaptic bursting activity, the perfusion medium was switched to a solution containing increased [K+]o (0.2 mM) and increased [Ca2+]o (6.4 mM) for ≈1 h produced bursting activity similar to that described previously (Fig. 1A). The bursts occurred every 10–30 s (mean interburst interval [IBI] 18.8 ± 1.1 s; n = 13). Each burst constituted a negative shift in the field potential (4.7 ± 0.5 mV in amplitude; n = 13) lasting between 2 and 10 s (mean duration 4.2 ± 1.2 s; n = 13). Superimposed on the depolarizing potential were large population spikes representing the synchronous firing of multiple neurons. Power spectrum analysis of this firing activity revealed a peak in the low gamma-frequency band range (28.7 ± 1.1 Hz; n = 13) with additional peaks at high frequencies (Fig. 1C). An instantaneous frequency plot of the interspike interval of a representative burst showed that during the initial stage of the burst, interspike frequency was relatively high, peaking at about 150 Hz. Subsequently, the spike frequency rapidly decayed before stabilizing in the gamma-frequency range (25–80 Hz; Fig. 1B). This pattern of population spike firing was described previously (Bikson et al. 2003a). Further increasing [K+]o to 8.4 mM resulted in an increase in interburst frequency, but no overall change in the spectral frequency profile of the individual bursts (Fig. 1D).

Having established the basic properties of this nonsynaptic form of synchronous neuronal activity, we sought to determine whether IA played a role in regulating this type of activity. Addition of the Kv7 channel modulator retigabine (10 μM) to the bathing medium, after the generation of stable bursting activity in area CA1, completely abolished all discernible activity (n = 3; Fig. 2). Retigabine is known to shift the voltage dependency of Kv7 channels such that open probability is increased at more hyperpolarized membrane potentials (Main et al. 2000; Rundfeldt and Netzer 2000; Tatulian and Brown 2003; Tatulian et al. 2001; Wickenden et al. 2000). Therefore we reasoned that in hippocampal neurons, retigabine was acting as a channel opener (Gu et al. 2005). To confirm this, we coapplied the Kv7 channel blocker XE991 (10 μM), after the abolition of bursting activity by retigabine. This reliably caused the reappearance of the depolarizing shifts characteristic of the nonsynaptic bursting activity (n = 3; Fig. 2).

Drugs

All compounds were made to the required concentration in aCSF and applied to the slice by the perfusion system. Retigabine was synthesized by the Medicinal Chemistry department at GlaxoSmithKline. Linopirdine and XE991 were purchased from Tocris Cookson (Bristol, UK).

RESULTS

To study the role of nonsynaptic mechanisms involved in synchronizing neuronal activity it is useful to isolate synaptically connected neurons. Removal of extracellular Ca2+ can produce this effect by preventing synaptic vesicle exocytosis, a process dependent on the influx of Ca2+ into the presynaptic bouton. By increasing neuronal excitability by raising extracellular K+ levels under nominally Ca2+ free conditions, a number of groups have described a nonsynaptic form of synchronized epileptiform activity (Haas and Jefferys 1984; Jefferys and Haas 1982; Taylor and Dudek 1982; Thuault et al. 2002; Xiong and Stringer 2001). We used similar methods to generate nonsynaptic bursting activity in area CA1 of rat hippocampal slices. Incubation of hippocampal slices in a medium containing reduced [Ca2+]o (0.2 mM) and increased [K+]o (6.4 mM) for ≈1 h produced bursting activity similar to that described previously (Fig. 1A). The bursts occurred every 10–30 s (mean interburst interval [IBI] 18.8 ± 1.1 s; n = 13). Each burst constituted a negative shift in the field potential (4.7 ± 0.5 mV in amplitude; n = 13) lasting between 2 and 10 s (mean duration 4.2 ± 1.2 s; n = 13). Superimposed on the depolarizing potential were large population spikes representing the synchronous firing of multiple neurons. Power spectrum analysis of this firing activity revealed a peak in the low gamma-frequency band range (28.7 ± 1.1 Hz; n = 13) with additional peaks at high frequencies (Fig. 1C). An instantaneous frequency plot of the interspike interval of a representative burst showed that during the initial stage of the burst, interspike frequency was relatively high, peaking at about 150 Hz. Subsequently, the spike frequency rapidly decayed before stabilizing in the gamma-frequency range (25–80 Hz; Fig. 1B). This pattern of population spike firing was described previously (Bikson et al. 2003a). Further increasing [K+]o to 8.4 mM resulted in an increase in interburst frequency, but no overall change in the spectral frequency profile of the individual bursts (Fig. 1D).
Interestingly, however, the bursts appeared qualitatively different from those observed under control conditions. Specifically, the bursts appeared to be longer in duration and the population spike firing activity appeared to be substantially altered.

In an attempt to quantitatively assess these effects a separate set of experiments were performed using the Kv7 channel blockers XE991 and linopirdine. Both XE991 and linopirdine have been shown to block Kv7 current in recombinant systems (Wang et al. 1998, 2000) and hippocampal neurons (Hu et al. 2002; Shah et al. 2002). After the appearance of stable bursting activity induced by the low Ca\(^2+\)/high K\(^+\) solution, either linopirdine or XE991 (both at a concentration of 10 \(\mu\)M) were added to the perfusion medium. Addition of either of these compounds significantly increased the mean duration of the depolarizing envelope (linopirdine 35 \(\pm\) 6% increase; XE991 108 \(\pm\) 6% increase; Fig. 3, A and B; \(n = 5\), \(P < 0.05\)). Furthermore, with respect to linopirdine a small, but significant, increase in the interburst frequency was observed, such that the inter-burst interval decreased from 22.4 \(\pm\) 1.2 s to 17.8 \(\pm\) 1.7 s (\(P < 0.05\), \(n = 5\)). However, following application of XE991 no significant change in the interburst frequency was observed (control IBI, 17.9 \(\pm\) 0.9 s; XE991 IBI, 16.5 \(\pm\) 1.8 s; \(P > 0.05\)). Furthermore, no change in the mean amplitude of the negative field potential deflection was detected, once the fast population spike activity had been filtered with a
low-pass filter at <1 Hz. Thus the mean filtered amplitude under control conditions was 4.7 ± 0.5 mV (n = 13), whereas after application of either linopirdine or XE991 the mean amplitudes were 5.7 ± 1.1 mV (n = 5, P > 0.05) and 5.2 ± 0.8 mV (n = 5, P > 0.05), respectively (Fig. 3, A and B). The effects of linopirdine or XE991 failed to reverse after washout of the compounds for ≤60 min.

The M-current plays a fundamental role in regulating neuronal firing, an thus it follows that pharmacological blockade of Kv7 channels may modulate the synchronous firing of populations of neurons observed in this nonsynaptic form bursting activity. To examine this, the extracellular recordings were subjected to a digital high-pass filter set at 5 Hz, to remove the large slow negative field potential deflections, characteristic of this form of activity, and, therefore isolate the fast oscillatory activity. Spectrographic analysis of individual bursts revealed high-frequency (<100 Hz) population spike activity in the initial portion of the burst that decayed to lower gamma-frequency (30–80 Hz) activity in the latter portion of the activity (Fig. 4, A and B). This data are consistent with the instantaneous frequency analysis performed above (Fig. 1). A cursory inspection of the extracellular traces revealed that bath application of either linopirdine or XE991 (10 µM) largely abolished the oscillatory activity, with the exception of the activity near the initial and midportion of the burst. This was not the case after application of either linopirdine or XE991 the mean lag times in the presence of linopirdine or XE991 were 7.6 ± 0.8 ms (141 ± 17 Hz; n = 5, P > 0.05) and 8.7 ± 0.2 ms (117 ± 4 Hz; n = 5, P > 0.05), respectively (Fig. 3, A and B). However, autocorrelations of 150-ms segments at the approximate midpoint of the bursts showed that, although under control conditions rhythmic gamma-frequency firing activity could be detected (mean lag time = 27.2 ± 2.3 ms equating to 41 ± 4 Hz; n = 10), after blockade of Kv7 channels, no rhythmic activity was observed (Fig. 4, C and D).

**DISCUSSION**

Since its discovery in 1980, it has become clear that $I_M$ is expressed in a wide range of neuronal cell types, both in the peripheral and central nervous system (Brown and Adams 1980; Selyanko and Sim 1998). Consequently, there has been a great deal of interest in generating pharmacological agents that modulate the activity of the channels underlying this current, for the treatment of a variety of neurological disorders, including cognitive impairment (Fontana et al. 1994; Gribkoff 2003), various pain states (Blackburn-Munro and Jensen 2003; Dost et al. 2004; Passmore et al. 2003), and epilepsy (Fatope 2001; Rostock et al. 1996; Tober et al. 1996). With respect to epilepsy, retigabine, an anticonvulsant currently under development, has been shown to shift the voltage activation curve of Kv7.2/7.3 channels, such that the hyperpolarizing M-current has increasing prominence at more negative membrane potentials (Main et al. 2000; Rundfeldt and Netzer 2000; Tatulian and Brown 2003; Tatulian et al. 2001; Wickenden et al. 2000), thus producing an effective dampening of neuronal excitability. Furthermore, retigabine has been shown to be effective at abolishing or significantly reducing bursting in a range of in vitro models of epileptiform activity (Armand et al. 1999, 2000; Dost and Rundfeldt 2000). In this study we have shown that retigabine abolishes a form of bursting activity that is independent of chemical synaptic transmission and is commonly used to model nonsynaptic mechanisms underlying epileptiform activity (Jefferys 1995).

During low Ca$^{2+}$/high K$^+$-induced bursting, hippocampal pyramidal neurons are depolarized by 10–20 mV (Haas and Jefferys 1984), moving the membrane potential into the range at which Kv7 channels are more active. Presumably, in the presence of retigabine, there is an increase in open probability of Kv7 channels at these depolarized membrane potentials (Tatulian and Brown 2003) leading to an increased K$^+$ conductance. The activation of this, or any other, K$^+$ channel with a similar I–V relationship would result in the hyperpolarization of hippocampal neurons, thus decreasing excitability. Nonsynaptic bursting was reinstated by the subsequent blockade of Kv7 channels, confirming that the actions of retigabine were likely to occur by these channels.

Because increasing the open probability of Kv7 channel led to the complete abolition of bursting activity, one might assume that blockade of these channels would result in an increase in bursting activity. Such an increase in activity is observed when [K$^+$] is increased (see also Haas and Jefferys 1984), which led to a positive shift in $E_{K}$, resulting in a

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**FIG. 2.** Activation of Kv7 channels abolished low Ca$^{2+}$/high K$^+$-induced bursting. Application of the Kv7 channel modulator N-(2-amino-4-(4-fluorobenzylamino)-phenyl)carboxylic acid ethyl ester (retigabine, 10 µM) abolished the large negative-going potential and the associated synchronous population spike firing. Further addition of the Kv7 channel blocker XE991 [10,10-bis(4-pyridinylmethyl)-9(10H)-anthracenone] restored the negative-going potentials, but not the population spike activity.
reduction in K\textsuperscript+ membrane conductance. However, despite the increase in interburst frequency in 8.4 mM [K\textsuperscript+]\textsubscript{o}, the spectral frequency profile of the intraburst oscillatory activity was similar to that observed in 6.4 mM [K\textsuperscript+]\textsubscript{o}. These data confirm earlier observations (Haas and Jefferys 1984). Interestingly, however, blockade of Kv7 channels produced quite different effects; thus interburst frequency was either unchanged or only slightly increased, but the extracellular synchronous population spike activity was largely abolished, especially in the gamma-frequency range.

To our knowledge this is the first report of M-current modulation of gamma-frequency–synchronous neuronal network behavior. This is perhaps surprising because mAChR agonists are well known to induce synaptically driven gamma-frequency oscillations (Brown et al. 2005; Fisahn et al. 1998, 2002; Mann et al. 2005). Furthermore, Kv7.2 channels are known to be expressed in key cellular locations for the control of synchronous oscillatory behavior (Cooper et al. 2001). Because activation of mAChRs is thought to lead to a reduction in the M-current, it follows that a direct closure of Kv7 channels might result in synaptically driven oscillatory activity. However, a recent report demonstrated that blockade of the M-current did not induce or prevent synaptic gamma-frequency activity (Fisahn et al. 2002). Furthermore, Fisahn and colleagues specifically show that, in fact, the M1 muscarinic acetylcholine receptor subtype does not couple to $I_M$ in hippocampal pyramidal neurons. With respect to other forms of neuronal network oscillations, there is some evidence of M-current control. For instance, Kv7.2 heterozygous knockout mice and Kv7.2 conditional knockout mice were both more susceptible to seizures (Peters et al. 2005; Watanabe et al. 2000). Furthermore, either pharmacological (Hu et al. 2002) or transgenic (Peters et al. 2005) blockade of M-channels suppressed an intrinsic theta frequency resonance behavior of CA1 pyramidal neurons. Interestingly, Peters and colleagues also show that CA1 neurons from mutant mice expressing a dominant negative form of the Kv7.2 subunit (resulting in impaired M-current activity) had biophysical properties that suggested

FIG. 3. Blockade of Kv7 channels alters the pattern of burst activity induced by low Ca\textsuperscript{2+}/high K\textsuperscript{+}. A: application of the Kv7 channel blocker 3,3-bis(4-pyridylmethyl)-1-phenylindolin-2-one (linopirdine, 10 μM) caused a small but significant decrease in interburst interval (IBI) and increase in burst duration. There was no significant effect on burst amplitude ($n = 5$). B: likewise, application of XE991 significantly increased burst duration, but not burst frequency or amplitude ($n = 5$).
hyperexcitability. For instance, neuronal input resistance was increased, whereas spike accommodation and the medium afterhyperpolarization (mAHP) were decreased. These data in particular suggest that Kv7 channel blockade results in a complex series of biophysical changes that are likely to feed into changes in the temporal regulation of neuronal behavior.

So what might be the role of the M-current in regulating/generating nonsynaptic gamma band synchronous neuronal network behavior? Recent reports suggest that the M-current plays an important role in the mAHPs that occur after action potentials in CA1 pyramidal neurons (Gu et al. 2005; Peters et al. 2005). Thus blockade of Kv7 channels results in a decrease in the hyperpolarizing influence of the mAHP, particularly at depolarized (>-60 mV) membrane potentials (Gu et al. 2005). As a result, one might expect neurons to show an increase in excitability in response to Kv7 channel blockers such as linopirdine and XE991. Indeed, we observed a significant increase in the duration of the negative-going potential associated with each burst in response to blockade of Kv7 channels. Clearly, however, intraburst firing activity was severely dis-

**FIG. 4.** Blockade of Kv7 channels abolished gamma, but not high-frequency, intraburst firing. A and B: traces show a single burst recorded under control conditions and another after application of 10 µM linopirdine (Lin) or 10 µM XE991. Traces were digitally high-pass filtered at 5 Hz to removed the slow negative potential and a spectrographic analysis was performed. Control spectrographs show an initial peak at >100 Hz, which rapidly decays into the gamma-frequency band. In the presence of Kv7 channel blockers, the gamma-frequency activity is abolished, but a high-frequency hot spot remains at the very beginning of the burst. C and D: traces are the boxed regions shown in A and B shown on an expanded timescale. Autocorrelelograms of these traces are shown below. Control traces are shown in black, whereas traces recorded in the presence of a drug are shown in red. Rhythmic gamma-frequency activity recorded at the approximate midpoint of the burst (seen in aii and bii) is abolished in the presence Kv7 channel blockers (aiv and biv).
ruptured. This suggests that the mAHP may play a fundamental role in the temporal organization of synchronous firing activity within localized neuronal networks.

Alternatively, because M-current blockade results in an increase in neuronal input resistance (Yue and Yarai 2004), the depolarizing envelope that is associated with each burst might be larger in amplitude. If this depolarization is sufficiently increased, this may result in the inactivation of Na⁺ currents crucial for neuronal action potentials (Bikson et al. 2003b). Although we cannot completely exclude this possibility, two lines of argument suggest that this does not occur. First the amplitude of the large extracellular negative-going potential associated with the bursts does not change in the presence of XE991 or linopirdine. Before this analysis, the traces were low-pass filtered at <1 Hz to eliminate the influence of the population spike firing on burst amplitude. This would tend to suggest that there was no overall increase in the amplitude of the intracellular depolarization in response to Kv7 channel blockade. Second, previous studies have suggested that Na⁺ channel activity is crucial for both the population spike firing and the large negative-going response (Bikson et al. 1999). Thus if Na⁺ channels were largely inactivating in response to an increased depolarization, this might be expected to shorten the burst duration, as occurs in the presence of increased [K⁺]₀, whereas in fact, burst duration increased in response to Kv7 channel blockade.

Gamma-frequency activity is widely proposed to be central to cognitive function, and consequently one might expect agents that disrupt gamma band activity to cause detrimental changes to learning and memory. Retigabine consistently abolished both the large regular low Ca²⁺/high K⁺-induced bursts and consequently their associated gamma-band activity. Although no substantial memory studies have been published with this agent it is reported to lack major effects on cognition at doses that produce anxiolytic behavior in vivo (Korsgaard et al. 2005). Blockers of Kv7 channels such as linopirdine and XE991 are reported to be cognitive enhancers, so it was somewhat unexpected to note the ability of both molecules to abolish field burst–associated gamma activity. It is worth noting here, however, that gamma oscillations driven with carbachol under more physiological conditions are resistant to Kv7 blockade (Fisahn et al. 2002). Furthermore, it should be noted that subthreshold synaptically driven gamma-frequency activity induced under physiological conditions is substantially different from the type of activity recorded here. Nonetheless, future studies of retigabine actions on neurophysiological activity recorded in vivo would be of some interest, particularly because this would provide information on how networks still wired to the rest of the CNS are modified by Kv7 channel modulation.

References


Haas HL, Jefferys JG, Slater NT, and Carpenter DO. Modulation of low calcium induced field bursts in the hippocampus by monoamines and cholinomimetics. Pfluegers Arch 400: 28–33, 1984.


Thuault SJ, Davies CH, Randall AD, and Collingridge GL. Group I mGluRs modulate the pattern of non-synaptic epileptiform activity in the hippocampus. *Neuropharmacology* 43: 141–146, 2002.


