RAPID REPORT

α5 subunit-containing $GABA_A$ receptors affect the dynamic range of mouse hippocampal kainate-induced gamma frequency oscillations *in vitro*

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Though all *in vitro* models of gamma frequency network oscillations are critically dependent on $GABA_A$ receptor-mediated synaptic transmission little is known about the specific role played by different subtypes of $GABA_A$ receptor. Strong expression of the α5 subunit of the $GABA_A$ receptor is restricted to few brain regions, amongst them the hippocampal dendritic layers. Receptors containing this subunit may be expressed on the extrasynaptic membrane of principal cells and can mediate a tonic $GABA_A$ conductance. Using hippocampal slices of wild-type (WT) and α5−/− mice we investigated the role of α5 subunits in the generation of kainate-induced gamma frequency oscillations (20–80 Hz). The change in power of the oscillations evoked in CA3 by increasing network drive (kainate, 50–400 nM) was significantly greater in α5−/− than in WT slices. However, the change in frequency of gamma oscillations with increasing network drive seen in WT slices was absent in α5−/− slices. Raising the concentration of extracellular GABA by bathing slices in the GABA transaminase inhibitor vigabatrin and blocking uptake with tiagabine reduced the power of gamma oscillations more in WT slices than α5−/− slices (43% *versus* 15%). The data suggest that loss of this $GABA_A$ receptor subunit alters the dynamic profile of gamma oscillations to changes in network drive, possibly via actions of GABA at extrasynaptic receptors.

(Received 2 July 2004; accepted after revision 23 July 2004; first published online 29 July 2004)
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Fast oscillations within the EEG gamma frequency band (20–80 Hz) arise in various cortical areas and are thought to play a role in certain forms of information processing (Singer & Gray, 1995). In the hippocampus they may be involved in aspects of learning and memory (Lisman & Idiart, 1995; Fell *et al.* 2001).

Gamma activity in the hippocampal formation requires inhibitory synaptic transmission mediated by $GABA_A$ receptors (Whittington *et al.* 1995; Fisahn *et al.* 1998; LeBeau *et al.* 2002). These receptors are composed of a number of gene family subunit proteins (Barnard *et al.* 1998; Bonnert *et al.* 1999), with the majority of native neuronal $GABA_A$ receptors containing a combination of at least one α, one β and one γ subunit (Pritchett *et al.* 1989; McKernan & Whiting, 1996). In recent years gene targeting techniques have clarified certain functions of individual subunits (McKernan *et al.* 2000). $GABA_A$ receptors containing the α5 subunit have an almost uniquely restricted expression pattern, being abundant extrasynaptically in the hippocampal CA1 and CA3 dendritic fields but only weakly expressed in other brain regions (Wisden *et al.* 1992; Fritschy & Mohler, 1995; Sur *et al.* 1999; Brunig *et al.* 2002; Ramos *et al.* 2004). The strong expression of this $GABA_A$ receptor subunit within the hippocampus is intriguing in view of the role of this structure in certain aspects of learning and memory processes (Eichenbaum, 2000) and mice devoid of α5-containing $GABA_A$ receptors exhibit superior performances in a water maze test of spatial learning (Collinson *et al.* 2002).

α5-containing $GABA_A$ receptors mediate a tonic inhibitory conductance similar to that previously described in hippocampal pyramidal neurones (Whittington *et al.* 1996; Bai *et al.* 2001) and dentate

© The Physiological Society 2004 DOI: 10.1113/jphysiol.2004.071191

gyrus granule cells (Nusser & Mody, 2002). The small amount of spillover of GABA necessary to activate a tonic conductance via α5-containing receptors may occur during the firing of interneurones in rhythmic oscillatory activity (Scanziani, 2000). The presence of a tonic GABAergic conductance has been shown to reduce the power of gamma frequency oscillations in the hippocampus (Whittington *et al.* 1996).

In this study, we employ transgenic mice with a disrupted α5 gene (α5−/−) and compare the properties of gamma frequency network oscillations elicited in slices prepared from these mice and their wild-type littermates.

Methods

The generation of mice deficient for the α5 subunit of the $GABA_A$ receptor has been previously described (Collinson *et al.* 2002).

Slice electrophysiology

Adult male mice (mixed background strain C57BL6–129SvEv; aged 9–39 weeks) deficient for the $GABA_A$ receptor α5 subunit (α5−/−) and their respective wild-type siblings were anaesthetized with inhaled isoflurane followed by injection of ketamine ($> 100\ mg\ kg^{-1}$) and xylazine ($> 10\ mg\ kg^{-1}$) I.P. Animals were perfused intracardially with ∼10 ml of modified artificial cerebrospinal fluid (ACSF) which was composed of (mM): 252 sucrose, 3 KCl, 1.25 NaH_2PO_4, 24 $NaHCO_3$, 2–4 $MgSO_4$, 2 $CaCl_2$ and 10 glucose. This procedure was in accordance with the UK Animals (Scientific Procedures) Act 1986. Horizontal slices 450 μm thick were prepared and were maintained at 34°C at the interface between warm/wetted 95% O_2–5% CO_2 and ACSF containing (mM): 3 KCl, 1.25 NaH_2PO_4, 2 $MgSO_4$, 2 $CaCl_2$, 24 $NaHCO_3$, 10 glucose and 126 NaCl. Data were recorded with an Axoprobe-1A amplifier (Axon Instruments Inc., Union City, CA, USA). Signals were filtered at 1 kHz and digitized at 10 kHz using an Instrutech ITC-16 A/D board (Instrutech Corp., NY, USA). AxoGraph 4.6 software (Axon Instruments Inc.) was used to analyse the data.

Overall structure of the network model

The programme used to simulate persistent gamma oscillations, in a network of multicompartment neurones, was as in Traub *et al.* (2003). The network contained 3072 pyramidal neurones and 384 interneurones, with each model neurone containing a soma, branching dendrites, and a segment of axon. The 'control' simulation had a between-interneurone gap junction conductance of 1.84 nS. The effects of extrasynaptic $GABA_A$ receptors were simulated by using a uniform density of tonic $GABA_A$ conductance over the dendrites of the pyramidal cells (reversal potential −15 mV relative to resting potential). Values of the total tonic $GABA_A$ conductance were 0 and 10 nS. In addition, a model of interneurone network gamma rhythms was generated in the absence of pyramidal cell input to interneurones and the above tonic GABA conductance was applied to interneurones alone.

Results

Comparison of kainate-induced gamma oscillations in WT and α5−/− slices

In order to assess the consequences of the loss of α5-containing $GABA_A$ receptors on neuronal network activity, gamma frequency network oscillations were elicited in slices prepared from WT and α5−/− mice. Nanomolar concentrations of the AMPA/kainate receptor agonist kainate (50–400 nM) were used to evoke a persistent gamma frequency population rhythm in a concentration-dependent manner (Fig. 1*A* and *B*). Incremental increases in agonist concentration yielded progressively larger amplitude network oscillations in WT slices up to 200 nM. Further increases in kainate concentration produced no further increase in power of the gamma oscillation. In α5−/− slices further increases in kainate concentration generated a greater power at gamma frequencies with the highest concentration tested (400 nM) generating oscillations with mean power double that in WT slices (Fig. 1*B*i). This increase in the maximum power of gamma frequency oscillations was significant ($P < 0.05$, $n = 6$, two-way analysis of variance). Such changes in power could be due to changes in fast synaptic inhibition onto pyramidal cells. However, analysis of the strength of monosynaptic, electrically elicited IPSPs in CA3 pyramidal cells revealed no significant difference ($P > 0.05$, $n = 7$) between WT and α5−/− tissue at all stimulus intensities tested (0–10 V, Fig. 1*B*ii). Figure 1*D* summarizes data from a simulation in which the basic features of kainate-evoked gamma oscillations in WT and α5−/− slices were reproduced. By setting the tonic $GABA_A$ conductance on pyramidal cell dendritic membranes to 10 nS (as a model for tissue from WT) and 0 nS (as a model for α5−/−) the enhanced power of gamma activity in α5−/− slices could be accurately replicated.

Despite the peak power of gamma frequency oscillations occurring at concentrations of kainate = 200 nM the frequency of the oscillations in slices from WT animals continued to increase throughout the concentration range used here. This effect was not seen in slices with no α5-containing GABA receptors. After superfusion of low concentrations of kainate, the peak frequency of gamma oscillations in WT and α5−/− slices was comparable.

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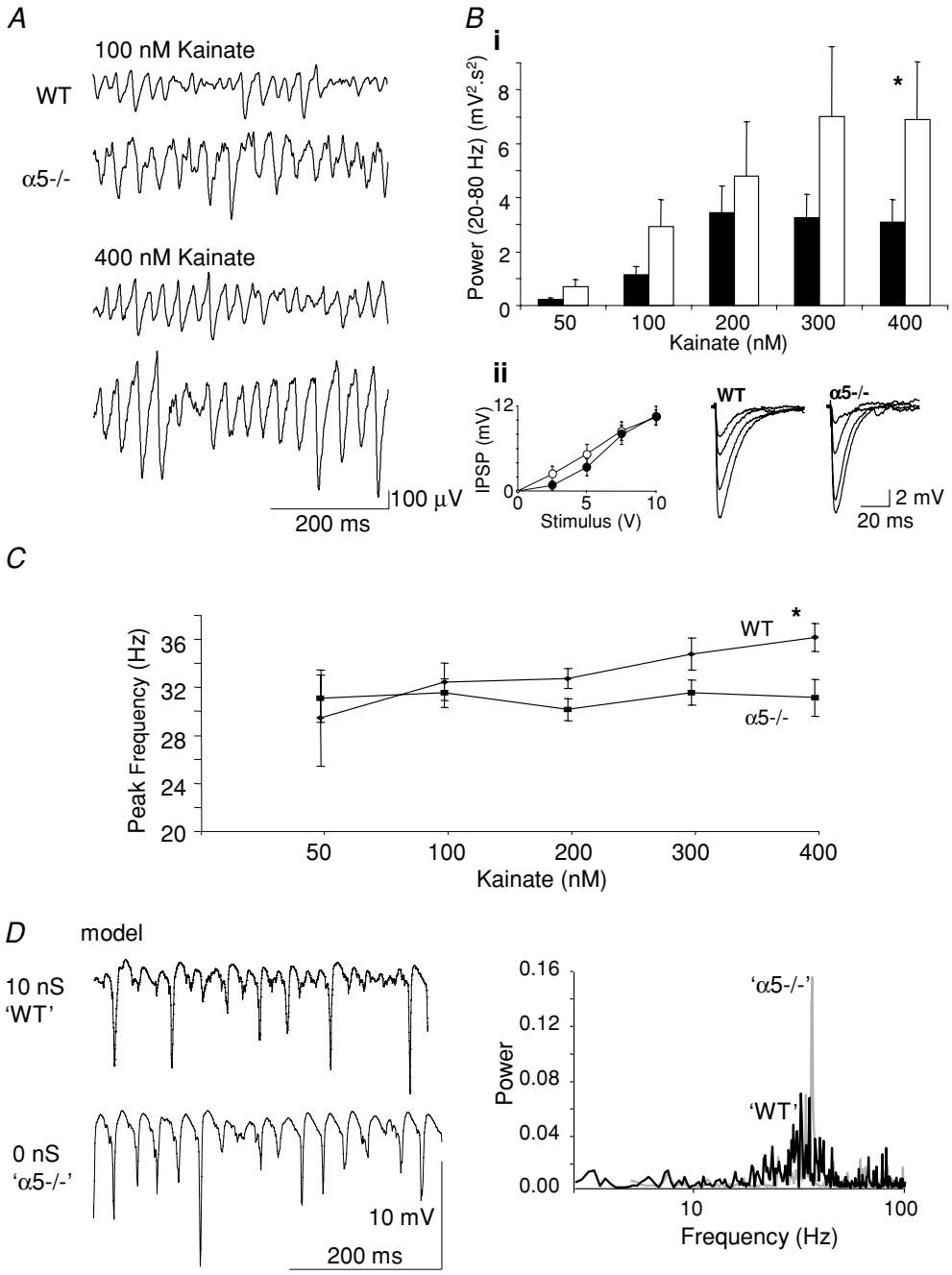

Figure 1. Effects of α5 subunit deletion on hippocampal population gamma oscillations induced by kainate

A, in wild-type (WT) and α5 knock-out (α5−/−) slices, superfusion with nanomolar concentrations of kainate (50–400 nM) resulted in the appearance of persistent gamma frequency network oscillations. The traces show extracellular field recordings from stratum radiatum of the CA3 area. *B*i, agonist concentration *versus* spectral power (20–80 Hz) relationship of kainate-induced gamma frequency oscillations in wild-type (black bars) and α5−/− (white bars) slices showing enhanced power change with network drive. Data shown as mean ± S.E.M., $n = 6$ for WT, $n = 7$ for α5−/−. *B*ii, monosynaptic evoked IPSPs from CA3 pyramidal cells at stimulus intensities from 0 to 10 V $n = 7$, WT (●) and α5−/− (○). *C*, mean ± S.E.M. frequency changes with increased kainate concentration were absent in α5−/− slices. *D*, network model replicates basic experimental features of kainate-evoked oscillations in WT and α5−/− slices. The effects of pyramidal cell extrasynaptic $GABA_A$ receptors on network oscillations was simulated using tonic GABA conductances of 10 nS ('WT', black trace) and 0 nS ('α5−/−', grey trace) on dendritic compartments. Traces show simulated 'field potential' data. Power spectra reveal that decreased tonic $GABA_A$ conductance resulted in an increase in the power of network oscillations.

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However, at higher concentrations, the peak frequency of gamma oscillations elicited by 400 nM kainate was unchanged in $\alpha5-/-$ slices but significantly increased in WT slices (WT median: 36.6 Hz; (interquartile range (IQR): 36.6, 34.2), $n = 6$; $\alpha5-/-$ median: 31.7 Hz; (IQR: 31.7, 31.7), $n = 7$; $P < 0.05$, Mann–Whitney rank sum test). Overall, the effect of kainate concentration on frequency change of gamma oscillations in WT and $\alpha5-/-$ slices was significantly different ($P < 0.05$, two-way analysis of variance, Fig. 1*C*).

Gamma oscillations generated in isolated interneurone networks in WT and $\alpha5-/-$ slices

In order to establish whether absence of $\alpha5$-containing GABA receptors was directly affecting interneurone networks we used a model of interneurone network gamma which did not rely on phasic interplay between principal cells and interneurones (Whittington *et al.* 1995). The inhibitory interneurone network was pharmacologically isolated from principal cell outputs by bath application of 50 mM D-AP5 (D-aminophosphonovalerate; NMDA receptor antagonist) and 20 mM NBQX (AMPA/kainate receptor antagonist). $GABA_B$ receptors were also blocked with 1 mM CGP55845. High molarity potassium solution (1.5 M KCH_3SO_4) was pressure-ejected onto stratum radiatum/lacunosum-moleculare of CA1 (Towers *et al.* 2002), and the oscillations were recorded in CA1 stratum radiatum (Fig. 2). Contrary to the increase in peak power of gamma oscillations seen in the persistent, kainate-induced, model of gamma oscillations, a decrease in the mean power of gamma oscillations was seen (WT: $5.09 \pm 1.78\ mV^2\ s^{-2}$, $n = 15$; $\alpha5-/-$: $2.83 \pm 0.59\ mV^2\ s^{-2}$, $n = 14$). However, this was not a significant effect ($P > 0.05$). There was no significant effect either on mean peak frequency of interneurone network gamma oscillations (WT: 48.7 ± 3.2 Hz, $n = 15$; $\alpha5-/-$: 45.1 ± 2.8 Hz, $n = 14$, $P > 0.1$) or rhythmicity of oscillations, measured as auto-correlation side peak amplitude (WT: 0.22 ± 0.02, $n = 14$; $\alpha5-/-$: 0.20 ± 0.02, $n = 14$, $P > 0.1$). In contrast the computational model predicted that extrasynaptic $GABA_A$ receptor-mediated conductance specifically on interneurones would serve to increase field power and decrease frequency from 52 Hz (conductance = 0.0 nS) to 32 Hz (conductance = 10 nS).

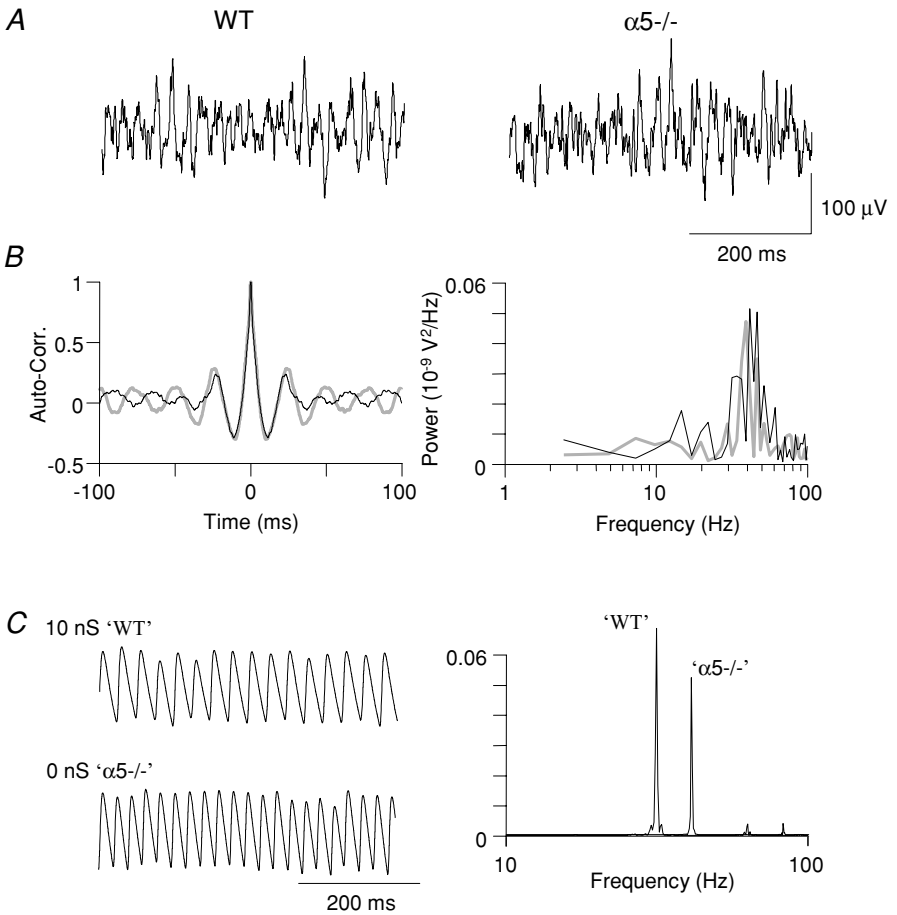

Figure 2. Interneurone network gamma oscillations elicited in the CA1 area of WT and $\alpha5-/-$ slices
A, example of interneurone network gamma oscillations (ING) elicited in CA1 of WT and $\alpha5-/-$ slices by pressure ejection of 1.5 M KCH_3SO_4 after superfusion of glutamate receptor blockers (50 μM D-AP5, 20 μM NBQX) and a $GABA_B$ receptor antagonist (1 μM CGP55845). *B*, corresponding pooled power spectra and auto-correlation data demonstrated that power, frequency and rhythmicity of the oscillations in both slices were not changed. *C*, model of interneurone network (synaptic connectivity between pyramidal cells and interneurones omitted from model used in Fig. 1). In contrast to the experimental data the model predicted large frequency changes in ING in the presence or absence of tonic GABA conductance. Data shown are 'field potential' recordings and corresponding power spectra.

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Consequences of raising extracellular [GABA] on oscillations in WT and α5−/− slices

To investigate whether the effects of α5-containing GABA receptors could be mediated by GABA overspill from synapses we increased extracellular GABA concentration. Gamma oscillations were generated as in Fig. 1 with kainate (200 nM) but with $GABA_B$ receptors blocked with CGP55845 (1 μM) to prevent any effects of GABA overspill on this receptor subtype. Application of the GAT-1 GABA uptake inhibitor tiagabine (20 μM) (Borden *et al.* 1994) generated a similar modest reduction in gamma power in both WT (to 88.6 ± 15.6% of control, $n = 9$) and α5−/− (to 74.2 ± 20.4% of control, $n = 5$) slices (data not shown). There was no significant difference between the two groups ($P > 0.05$). Further elevation of extracellular GABA concentration by *preincubation* with the GABA transaminase inhibitor vigabatrin (200 μM), before tiagabine application, produced a significantly greater decrease in gamma power in slices from WT compared with α5−/− animals (Fig. 3). Following vigabatrin preincubation (90 min), a significantly greater reduction in the power of oscillations in WT slices than in α5−/− slices was observed 30 min after subsequent tiagabine application (WT: 42.9 ± 6.1%, $n = 11$; α5−/−: 14.7 ± 7.3%, $n = 8$; $P < 0.01$, *t* test; Fig. 3). As with tiagabine alone, there

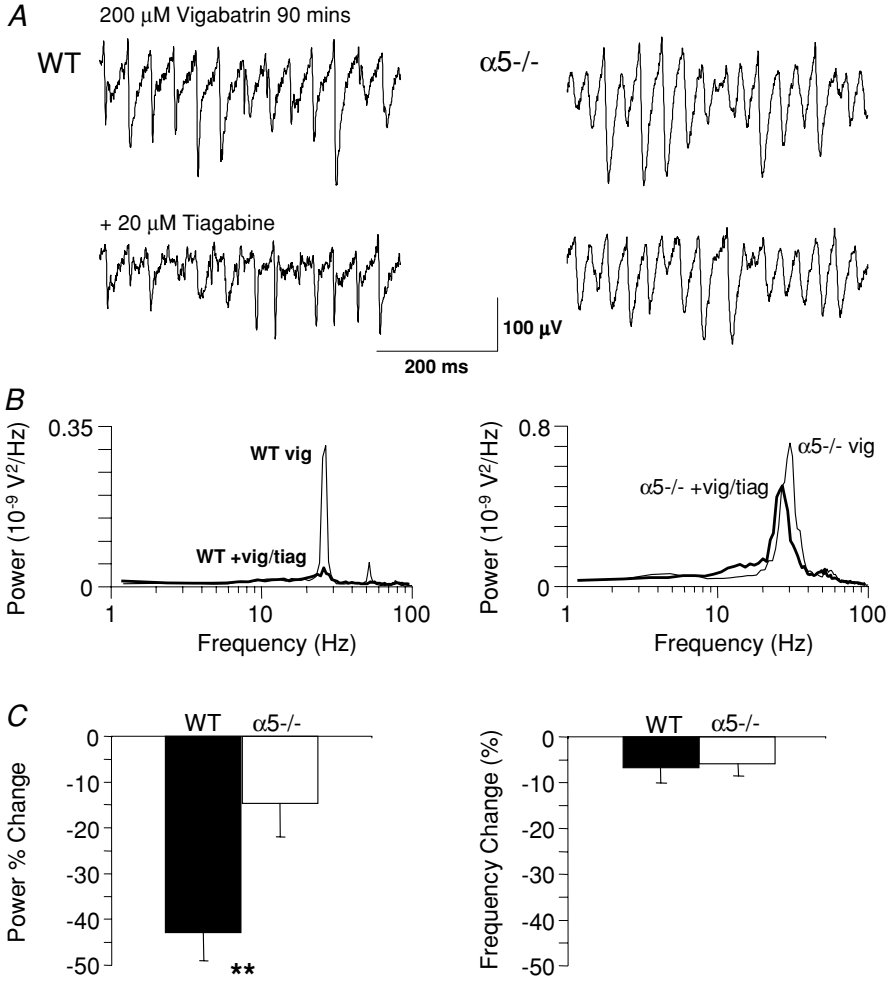

Figure 3. Elevated concentrations of $[GABA]_o$ reduce the power of gamma oscillations less in α5−/− slices than in WT slices

A, example of kainate-evoked oscillations after superfusion of 200 μM vigabatrin for 90 min, and after subsequent block of GABA uptake with tiagabine (20 μM). *B*, corresponding power spectra indicate a substantial reduction in power of the oscillations in the WT slices and a smaller reduction in the α5−/− slices. Thin lines = vigabatrin control; thick lines = vigabatrin + tiagabine. *C*, group data demonstrating the change in power (20–80 Hz) and peak frequency of oscillations in WT (black bars) and α5−/− slices (white bars) after tiagabine application (expressed as percentage change from control). Tiagabine application resulted in a significantly larger reduction in the power of oscillations in WT compared to α5−/− slices (**$P < 0.01$, *t* test).

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was no significant difference in the effect of vigabatrin alone on gamma oscillations ($P > 0.05$). This effect was accompanied, in both sets of slices, by a small, comparable reduction in oscillation peak frequency (WT: $6.7 \pm 3.4\%$, $n = 14$; $\alpha5-/-$: $5.9 \pm 2.6\%$, $P > 0.1$, $n = 11$).

Discussion

Alterations in dynamic range of oscillations in $\alpha5-/-$ slices

This study provides the first insight into the role of a specific $GABA_A$ receptor subunit protein in the generation of hippocampal network oscillations. The mean peak power of kainate-induced gamma oscillations in hippocampi devoid of $\alpha5$ subunit-containing $GABA_A$ receptors was higher than in the WT. This finding was accompanied by no significant change in the strength of fast $GABA_A$ receptor-mediated monosynaptic inhibitory events in principal cells, implying that during rhythmic network oscillations, activation of these receptors by increased ambient GABA mediates a predominantly tonic inhibitory conductance that serves to limit the change in power of gamma activity in response to increasing network drive. In contrast, gamma oscillations in WT slices showed a change in frequency with increasing network drive that was absent in $\alpha5-/-$ slices. Thus, the presence of $\alpha5$ subunit-containing $GABA_A$ receptors appeared to limit increases in gamma power while facilitating an increase in gamma frequency in response to increased network excitation in this model. In the absence of these receptors, increased network drive is represented as an increase in gamma power only. Power of these field oscillations is dependent upon the local potential changes generated by synchronous synaptic inputs to pyramidal cells. For a given synaptic conductance a smaller field response would be seen with a lower membrane resistance. Thus, in the case of phasic IPSPs underlying gamma oscillations, an accompanying tonic GABAergic conductance would reduce the influence of these IPSPs on principal cells and reduce the relative power of the consequent field. The frequency of gamma rhythms is dependent on the kinetics and amplitude of phasic inhibition. Collinson *et al.* (2002) showed that the bi-exponential decay in WT mice was seen to a lesser extent in $\alpha5-/-$ mice. Given this we suggest that the more labile frequency dynamics in WT mice may come from the relative proportions of the fast and slow decays with changing levels of GABA release as network drive increases. Some confusion exists as to the extent of involvement of the $\alpha5$ subunit in phasic synaptic responses. Collinson *et al.* (2002) demonstrated a significant decrease in small, spontaneous IPSCs but not the 5- to 10-fold larger evoked responses. Caraiscos *et al.* (2004) also reported no change in larger IPSCs. This difference may reflect the high affinity of GABA for $\alpha5$-containing receptors, with relatively small amounts of GABA release preferentially activating these receptors over those containing other α subunits. With larger amounts of GABA release the higher number of non-$\alpha5$-containing subsynaptic receptors may make the majority contribution to postsynaptic currents.

As kainate-induced persistent gamma oscillations are generated by an interplay between principal cells and populations of interconnected interneurones, the rhythmicity of the network oscillation could theoretically have been impaired by any reduction in the coherence of interneurone output onto principal cells, caused by removal of a subset of interneurone-expressing α subunits. However, two observations suggest this was not the case. Firstly the power and frequency of oscillations generated in pharmacologically isolated interneurone networks (interneurone network gamma) was unchanged in $\alpha5-/-$ slices. Secondly, the model predicted that inclusion of an $\alpha5$-like conductance in interneurones would markedly affect the frequency of interneurone network rhythms. The experimental interneurone network gamma more closely resembled the model data in frequency when a tonic GABA conductance was present on interneurones. A tonic GABAergic influence on interneurones has been demonstrated to control interneurone excitability (Semyanov *et al.* 2003). However, $\alpha5$ expression has been found in specific interneurone subtypes in early postnatal hippocampus (Ramos *et al.* 2004) but not in adult tissue, and there was no difference in the nature of the interneurone network rhythm when comparing tissue from WT and $\alpha5-/-$ mice. Thus the repertoire of interneurone $GABA_A$ receptor α subunits appeared to be little affected in slices from adult $\alpha5-/-$ mice.

Differential change in the power of gamma oscillations in WT and $\alpha5-/-$ slices after increasing extracellular [GABA]

In addition to studies suggesting that $\alpha5$ subunit-containing $GABA_A$ receptors may have a predominantly extrasynaptic location (Brunig *et al.* 2002; Crestani *et al.* 2002) it has recently been reported that these receptors can be activated by low concentrations of GABA and mediate a form of tonic inhibition in hippocampal pyramidal neurones (Caraiscos *et al.* 2004). These results suggest therefore that spillover of synaptically released GABA during the generation of gamma oscillations is sufficient to activate a tonic $\alpha5$-mediated conductance on pyramidal neurones. After using vigabatrin as a tool to raise the concentration of GABA in the tissue, blockade of GABA uptake reduced the power of the oscillatory activity to a significantly greater degree in WT slices. This provides support for the idea that $\alpha5$-containing $GABA_A$ receptors in the hippocampus are activated by the synchronous release of GABA during rhythmic oscillations thus mediating a persistent tonic conductance that in

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turn governs the amplitude of the emergent activity. This hypothesis was supported by model simulations in which reducing the tonic $GABA_A$ conductance on the dendritic membrane of principal cells from 10 to 0 nS accurately reproduced the enhanced peak gamma power in $\alpha5-/-$ slices.

This study indicates that $\alpha5$ subunit-containing $GABA_A$ receptors affect the dynamic response of hippocampal gamma rhythms to changes in network drive. The enhanced power of gamma oscillations in $\alpha5-/-$ slices may be due to removal of a population of $\alpha5$-containing $GABA_A$ receptors that mediate a tonic inhibition of principal cell dendrites. This change in power was accompanied by an increased stability of the oscillation in the frequency domain. Since it is the temporal characteristics of network rhythms that have been proposed to underlie their role in neuronal network function it is of note that recent studies have described the pro-cognitive effects of either removal or inverse agonism of this receptor (Collinson *et al.* 2002; Chambers *et al.* 2003).

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Acknowledgements

This work was supported by The Medical Research Council, UK and The Wellcome Trust.

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