View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Neuron, Vol. 34, 635–646, May 16, 2002, Copyright ©2002 by Cell Press

A Presynaptic Kainate Receptor Is Involved in Regulating the Dynamic Properties of Thalamocortical Synapses during Development

Fleur L. Kidd, Urania Coumis, Graham L. Collingridge, John W. Crabtree, and John T.R. Isaac[1]
MRC Centre for Synaptic Plasticity
Department of Anatomy
University of Bristol
Bristol BS8 1TD
United Kingdom

Summary

Previous studies have shown that pharmacological activation of presynaptic kainate receptors at glutamatergic synapses facilitates or depresses transmission in a dose-dependent manner. However, the only synaptically activated kainate autoreceptor described to date is facilitatory. Here, we describe a kainate autoreceptor that depresses synaptic transmission. This autoreceptor is present at developing thalamocortical synapses in the barrel cortex, specifically regulates transmission at frequencies corresponding to those observed in vivo during whisker activation, and is developmentally down regulated during the first postnatal week. This receptor may, therefore, limit the transfer of high-frequency activity to the developing cortex, the loss of which mechanism may be important for the maturation of sensory processing.

Introduction

The short-term dynamic properties of cortical synapses are thought to be critically important for the processing of information by cortical circuits (Abbott et al., 1997; Tsodyks and Markram, 1997; Markram et al., 1998). Synapses that exhibit short-term depression are thought to signal a change in the rate of presynaptic activity to the postsynaptic neuron, while nondepressing synapses signal information about the absolute firing rate. Therefore, the mechansisms that regulate these dynamic properties are important for determining information processing in cortical circuits. Recently, it has been shown that experience modifies the dynamic properties of synapses in the barrel cortex (Finnerty et al., 1999; Finnerty and Connors 2000); however, the mechanism(s) for this modulation is unknown.

One mechanism for the regulation of short-term plasticity at glutamatergic synapses that has received considerable attention recently is the presynaptic kainate receptor (Kullmann, 2001; Lerma et al., 2001; Schmitz et al., 2001b). Pharmacological activation of presynaptic kainate receptors has been shown to regulate glutamatergic synapses in the CA1 region of the hippocampus (Chittajallu et al., 1996; Kamiya and Ozawa, 1998; Vignes et al., 1998; Frerking et al., 2001) and at the mossy fiber-CA3 synapse (Vignes et al., 1998; Bortolotto et al., 1999; Contractor et al., 2000; Kamiya and Ozawa, 2000; Schmitz et al., 2000, 2001b; Lauri et al., 2001b). However, the physiological properties of these presynaptic receptors are not well understood. While knockout studies have indicated a physiological role for presynaptic kainate receptors in the hippocampus (Contractor et al., 2000, 2001), only recently has there been a direct demonstration of the physiological activation of a kainate autoreceptor (i.e., a presynaptic kainate receptor activated by the synaptic release of glutamate from the same pathway; Lauri et al., 2001a; Schmitz et al., 2001a). Despite the pharmacological evidence that presynaptic kainate receptors exist at other glutamatergic synapses (Lerma et al., 2001) and the widespread expression of kainate receptor subunits in the CNS (Bahn et al., 1994; Bettler and Mulle 1995), it remains to be determined whether presynaptic kainate receptors act as autoreceptors at other glutamatergic synapses. Furthermore, it is not known whether kainate autoreceptors can inhibit transmitter release in addition to the facilitatory role already described at the mossy fibers.

Here, we show that early in development (postnatal day [P]3–P6), a kainate autoreceptor mediates a form of short-term depression at thalamocortical synapses in response to brief trains of activity. This presynaptic receptor depresses transmission at high frequencies (e.g., 100 Hz). At lower frequencies (10–33 Hz), a depression also occurs, but this is not caused by the same receptor. This frequency-dependent distinction in the mechanism of depression may be significant because it corresponds to two bands of frequencies of activity observed in vivo during sensory stimulation, with $\geq$50 Hz corresponding to sensory-evoked activity and $\leq$33 Hz corresponding to activity in the absence of sensory stimulation (e.g., Nicolelis and Chapin, 1994). The presynaptic kainate receptor is developmentally regulated such that by the end of the first postnatal week, presynaptic kainate receptor function is no longer evident. However, in contrast, the depression at lower frequencies remains constant over this age range. These data indicate that early in development, a presynaptic kainate receptor specifically regulates the transfer of high-frequency activity to the barrel cortex. The loss of this mechanism by the end of the first postnatal week may allow the transfer of high-frequency, sensory-evoked activity from the thalamus to the cortex and, so, could be an important step in the maturation of sensory processing.

Results

Developing Thalamocortical Synapses Exhibit Short-Term Depression over a Range of Frequencies

In vivo recordings of activity in the ventral posterior medial nucleus (VPM), the thalamic nucleus that relays information from the whiskers to the barrel cortex, show that VPM neurons fire at frequencies of between 50 and $>$200 Hz in response to whisker activation (e.g., Nicolelis and Chapin, 1994). This activity is short lasting, consisting of a small number of action potentials

[1]Correspondence: j.t.r.isaac@bris.ac.uk

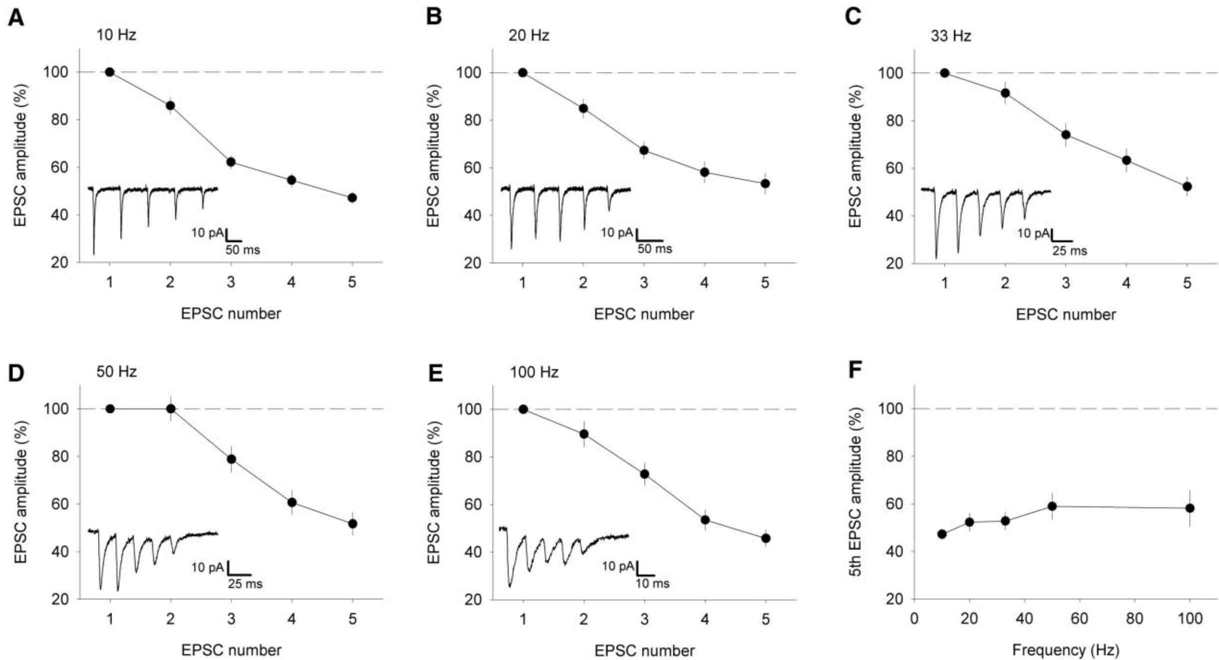

Figure 1. Thalamocortical Synapses in Developing Barrel Cortex Exhibit Short-Term Depression over a Range of Frequencies

(A) Summary data for EPSC amplitude (normalized to the amplitude of the first EPSC in the train) during a train of five stimuli at 10 Hz (n = 45). Inset: an example response to train stimulation (stimulus artifacts digitally removed).

(B–E) Summary data for trains at: (B) 20 Hz (n = 50), (C) 33 Hz (n = 58), (D) 50 Hz (n = 33), and (E) 100 Hz (n = 42). All traces are from the same cell.

(F) Amplitude of the fifth EPSC in the train (percentage of the first EPSC) as a function of train stimulation frequency (mean age = 5.9 ± 0.2 days, range = 3–8; n = 83 cells).

(typically, <5). In the absence of whisker activation, VPM neurons fire at lower frequencies. To investigate the synaptic mechanisms involved in the development of the transmission of sensory-evoked activity from VPM to the barrel cortex, we used whole-cell, patch-clamp recordings from neurons in layer IV of the barrel cortex in thalamocortical slices obtained from animals aged between P3 and P8 (Agmon and Connors, 1991; Crair and Malenka, 1995; Feldman et al., 1998; Kidd and Isaac, 1999). This is an age range that coincides with the critical period for experience-dependent plasticity at thalamocortical synapses in the barrel cortex (Fox, 1995).

Stimulation of thalamocortical axons with brief trains at 10, 20, and 33 Hz produced a depression in the amplitude of excitatory postsynaptic currents (EPSCs) during the train (Figures 1A–1C) similar to that previously shown for thalamocortical synapses (Gil et al., 1997, 1999). At 50 and 100 Hz, a depression in EPSC amplitude was also observed, which was very similar to that observed for the lower frequencies (Figures 1D–1F). Therefore, at this early developmental period, thalamocortical synapses exhibit very similar dynamic properties over a wide range of frequencies.

A Presynaptic Kainate Receptor Inhibits Transmission at Thalamocortical Synapses

Presynaptic kainate receptors regulate the properties of glutamatergic synapses in the hippocampus (Lerma et al., 2001; Schmitz et al., 2001b), and there is a high level of kainate receptor mRNA expression in rat sensory thalamus during the first week of life (Bahn et al., 1994). Therefore, we investigated whether a presynaptic kainate receptor is involved in the modulation of transmission at thalamocortical synapses. ATPA (1 μM), a selective kainate receptor agonist (Clarke et al., 1997; Cossart et al., 1998; Thomas et al., 1998), caused a reversible depression of the amplitude of thalamocortical EPSCs evoked by single-shock stimulation (Figure 2A). This depression was not associated with any change in conductance in the postsynaptic neuron (Figure 2A). We have recently reported that thalamocortical EPSCs are mediated by a fast AMPA receptor-mediated component and a slow kainate receptor-mediated component that can be reliably separated using a double exponential fit of the EPSC decay (Kidd and Isaac, 1999). Using this method of analysis, we found that ATPA caused a similar depression in both the AMPA and kainate receptor-mediated components of the EPSC (Figures 2B and 2C). These findings suggest that ATPA (1 μM) acts at a presynaptic kainate receptor at thalamocortical synapses and also has no effect on kainate receptors present on the postsynaptic neuron. In further support of this, ATPA also caused a change in short-term plasticity during a 100 Hz train (Figure 2D). Together, these data are consistent with ATPA acting at a presynaptic kainate receptor to cause a decrease in the probability of glutamate release and are inconsistent with ATPA acting at a postsynaptic locus.

It has been suggested recently that some of the effects of ATPA at hippocampal mossy fiber-CA3 syn-

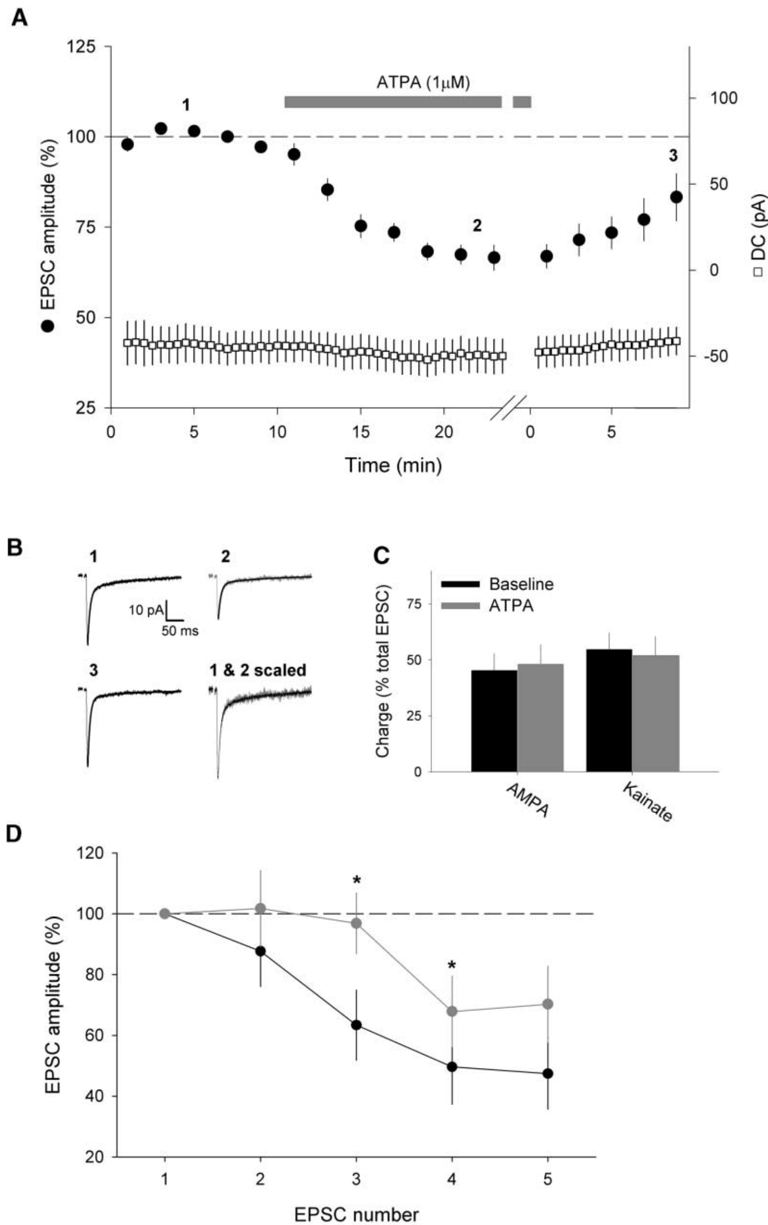

Figure 2. The Selective Kainate Receptor Agonist ATPA Depresses Transmission at Thalamocortical Synapses

(A) Summary data showing the effect of ATPA (1 μM) on EPSC amplitude (normalized to predrug baseline) evoked at 0.1–0.2 Hz (n = 16) and on holding current (DC; n = 9 cells). Data are for P5 and P6, only throughout this figure.

(B) EPSCs from a single experiment, as in (A), collected at the times indicated (black superimposed lines are double exponential fits of EPSC decay). Throughout this figure, gray represents data collected in the presence of ATPA.

(C) Summary data for the effect of ATPA on the charge transfer (percentage of the total EPSC charge) through the AMPA receptor and kainate receptor-mediated components of the EPSC (n = 16).

(D) Pooled data for the effect of ATPA on EPSC amplitude during a five stimulus, 100 Hz train (n = 9; *$p < 0.05$).

apses can be attributed to its actions on inhibitory interneurons, thereby causing release of GABA, which then activates inhibitory presynaptic $GABA_B$ receptors present on glutamatergic terminals (Schmitz et al., 2000; but see Lauri et al., 2001b). We addressed this possibility using the selective $GABA_B$ receptor antagonist CGP55845A (Davies et al., 1993). In the presence of CGP55845A (1 μM), ATPA caused a similar amount of depression of synaptic transmission, compared to that in the absence of the antagonist (Figure 3A). This lack of effect of CGP55845A on the ATPA-induced depression is not surprising since it has been demonstrated that $GABA_B$ receptors do not regulate transmission at thalamocortical synapses (Gil et al., 1997). Taken together, all of these data strongly suggest that the effects of ATPA are due to its acting on a presynaptic kainate receptor present at thalamocortical synapses. This suggests that transmission at thalamocortical synapses can be regulated by a presynaptic kainate receptor.

The Presynaptic Kainate Receptor Selectively Regulates Transmission during 50 and 100 Hz Trains

To investigate if presynaptic kainate receptors can be activated physiologically by synaptically released glutamate, we used the selective kainate receptor antagonist LY382884. Previous work has shown that LY382884 is selective for kainate receptors over AMPA and NMDA receptors in recombinant systems and cultured neurons (Bortolotto et al., 1999). In hippocampal slices (at a concentration of 10 μM,) it blocks kainate receptors, but does not block NMDA, AMPA, or mGlu receptors (Bortolotto et al., 1999; Lauri et al., 2001a) or the depression in excitatory transmission caused by carbachol, baclofen, or adenosine (Lauri et al., 2001b).

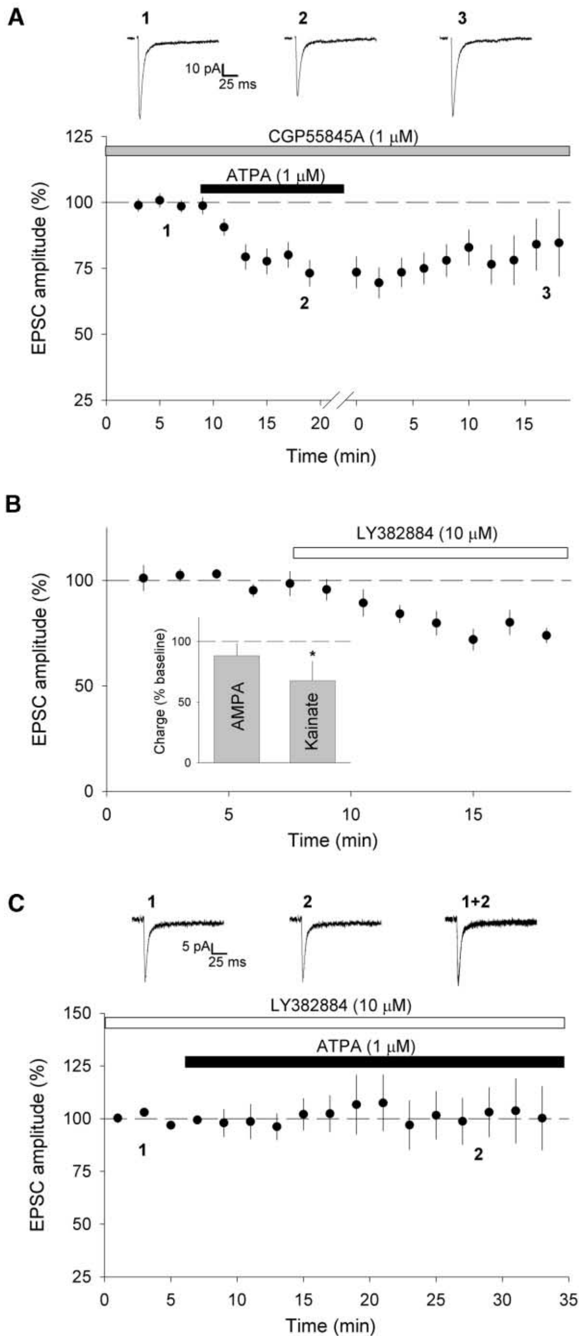

Figure 3. The Effects of ATPA Are Not Blocked by the $GABA_B$ Receptor Antagonist CGP55845A but Are Blocked by the Selective Kainate Receptor Antagonist LY382884

(A) Summary data for EPSC amplitude (normalized to baseline) versus time for experiments in which ATPA (1 μM) was applied in the presence of CGP55845A (1 μM; n = 17; data from P5 and P6). Inset: averaged EPSCs (ten consecutive responses) from an example experiment taken at the times indicated.

(B) Summary data for experiments showing the effect of LY382884 (10 μM) on single stimulus-evoked EPSC amplitude (n = 11; data from P5–P7). Inset: charge carried by the AMPA and kainate receptor-mediated components in the presence of LY382884 (percentage of baseline).

(C) Summary data for the effects of ATPA in the presence of LY382884 (n = 4; data from P4–P6). Inset: averaged EPSCs (ten consecutive responses) from an example experiment taken at the times indicated.

We first studied the effects of LY382884 on thalamocortical EPSCs evoked by single-shock stimulation. LY382884 (10 μM) caused a small depression in peak EPSC amplitude (Figure 3B). This was due to a partial block of the postsynaptic kainate receptors underlying the kainate receptor-mediated component of the EPSC, but LY382884 (10 μM) had no consistent effect on the AMPA receptor-mediated component of the EPSC (Figure 3B). We then investigated whether LY382884 blocks the effects of ATPA. When ATPA (1 μM) was applied in the presence of LY382884 (10 μM), there was no depression in synaptic transmission (Figure 3C), demonstrating that LY382884 (10 μM) blocks presynaptic kainate receptors at thalamocortical synapses.

The pharmacological activation of the presynaptic kainate receptor demonstrates that it can regulate transmission at developing thalamocortical synapses. However, these data do not indicate what the physiological function of this receptor may be. To investigate this, we studied the effects of LY382884 on the depression of EPSCs during the trains. LY382884 (10 μM) blocked the depression caused by five stimuli at 100 Hz (Figures 4A and 4B). The block of the depression was evident by the second response in the train (depression of second EPSC: control = 73% ± 9%, LY382884 = 95% ± 11%; $p < 0.05$, n = 12), indicating that the effect of kainate receptor activation was very rapid (i.e., within 10 ms). A similarly rapid effect of presynaptic kainate receptor activation has recently been reported for mossy fiber-CA3 transmission (Lauri et al., 2001a; Schmitz et al., 2001a).

The effects of LY382884 were frequency dependent. LY382884 had less of an effect during the 50 Hz trains, causing a partial reduction in the depression by the fifth stimulus (Figure 4D). However, LY382884 had no effect on the depression in response to trains at 33, 20, or 10 Hz (Figures 4C and 4D). The block of short-term depression at 100 Hz and 50 Hz by LY382884 cannot be attributed to its effects on postsynaptic kainate receptors for several reasons. (1) The effects of postsynaptic summation were removed during the analysis (see Experimental Procedures). (2) LY382884 partially blocks the kainate receptor-mediated EPSC, and this would produce an even greater depression due to reduced postsynaptic summation if the effects of postsynaptic summation were not removed.

We also performed experiments to investigate the mechanism of the depression at low frequencies. An inhibitory presynaptic mGluR regulates transmission at mossy fiber-CA3 synapses (Scanziani et al., 1997). Therefore, we investigated whether the LY382884-insensitive component to depression was due to this mechanism. However, the amount of depression at all frequencies was unaffected by the broad-spectrum mGluR antagonists CCPG (300 μM) and MCPG (500 μM) in combination (n = 8; data not shown) or by the broad-spectrum antagonist LY341495 (100 μM; n = 5; data not shown). This suggests that a presynaptic mGluR is not

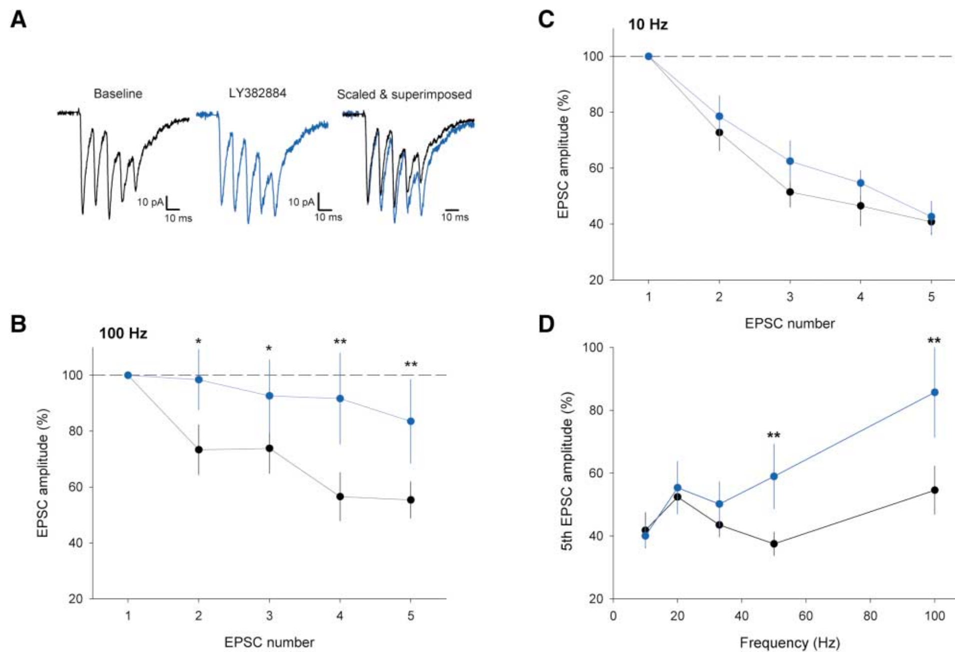

Figure 4. The Synaptic Activation of the Presynaptic Kainate Receptor Causes Depression during 100 Hz and 50 Hz Trains, but Not at Lower Frequencies

(A) EPSCs from a single experiment in which 100 Hz trains were applied before and during the application of LY382884 (10 μM).

(B) Summary data of EPSC amplitude (percentage of first EPSC in the train; n = 12; *p < 0.05, **p < 0.01; for this and subsequent figures, blue indicates LY382884 data).

(C) Summary data for the effects of LY382884 on 10 Hz trains (n = 7).

(D) Summary data of amplitude of the fifth EPSC in the train as a function of frequency for baseline and in the presence of LY382884 (100 Hz, n = 12; 50 Hz, n = 9; 33 Hz, n = 9; 20 Hz, n = 9; and 10 Hz, n = 7).

involved in regulating transmission at developing thalamocortical synapses.

Taken together, these data show that the presynaptic kainate receptor at developing thalamocortical synapses can be synaptically activated but that it only regulates transmission at the highest frequencies tested (50 and 100 Hz). Interestingly, these frequencies correspond to the frequencies of activity specifically associated in vivo with the activation of the whiskers (e.g., Nicolelis and Chapin, 1994).

A Model of Short-Term Plasticity at Developing Thalamocortical Synapses

We used modeling to further understand the mechanisms generating the depression over the 10–100 Hz frequency range (Figure 5). The experimental data are well described by a model in which a single synaptic activation produces two components of depression: one rapid, short-lasting, and kainate receptor-dependent and the other delayed and long-lasting (Figure 5A). The kinetics of the fast component were modeled based on the reported rapid activation of the presynaptic kainate receptor at the mossy fiber-CA3 synapse (Lauri et al., 2001a; Schmitz et al., 2001a). The slow, delayed component was modeled based on the kinetics of receptor-activated G protein-mediated inhibition of release at CA1 synapses (Davies and Collingridge, 1996). The blockade of the presynaptic kainate receptor was simulated by removing the rapid component of depression.

In this model, the rapid component of depression is activated instantaneously but is short lasting (Figure 5A). Therefore, only if the synapse is activated again within $\sim$10 ms are the effects of this component of depression evident (Figure 5B). In contrast, the slow component, due to its delayed onset and slow rise, only causes a small component to the depression during 100 Hz stimulation, which appears toward the end of the train of five stimuli. Therefore, removal of the rapid component (simulating the effects of the LY382884) removes the depression at 100 Hz early in the train, leaving a small depression intact later in the train (Figure 5C).

At 33 Hz, by the time each stimulus occurs, the preceding rapid component of depression has almost completely decayed (Figure 5D). Therefore, the depression is almost entirely mediated by the slower delayed mechanism at this and lower frequencies, and removal of the rapid component has little effect on the depression (Figure 5E). Thus, the differences in the kinetics of onset and duration of effect of these two components produce a differential frequency-dependent regulation of transmission and accounts for the observed frequency-dependent effects of LY382884 on the EPSC trains.

The Presynaptic Kainate Receptor Regulates Transmission at Close to Physiological Temperatures

The properties of the autoreceptor are likely to be influenced by temperature. For example, the kinetics of the receptor are likely to be temperature sensitive, and the patterns of activity that can drive it may be influenced by temperature, since glutamate transport and diffusion

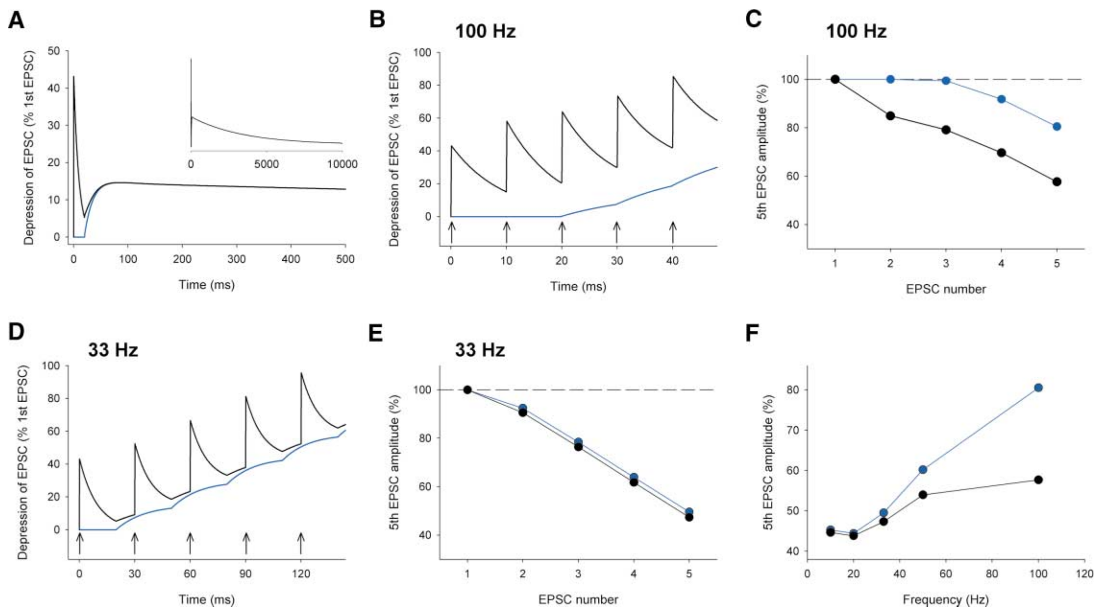

Figure 5. A Model with Two Kinetically Distinct Components of Depression Simulates the Experimentally Observed Depression at Thalamocortical Synapses and the Effects of LY382884

(A) The waveform describing the depression of release, resulting from a single synaptic activation (depression waveform), is represented as the depression of EPSC amplitude (percentage of first EPSC amplitude). Black trace: control conditions consisting of two components: a rapidly decaying component with instantaneous onset and single exponential decay (decay time constant [τ_{fast}] = 9.4 ms, peak depression [C_{fast}] = 43.7%) and a delayed slow component rising with a single exponential and decaying biexponentially (latency = 20 ms, τ_{rise} = 16.7 ms, τ_{slow1} = 34.7 ms, C_{slow1} = 4.0%, τ_{slow2} = 3436.4 ms, and C_{slow2} = 13.7%). Blue trace: the depression waveform with the rapid component removed to simulate pharmacological blockade of the presynaptic kainate receptor. Inset: the same waveforms on a longer timescale.

(B) Summation of the depression waveform during 100 Hz stimulation under control conditions (black) and in the absence of the rapid component (blue). Arrows indicate the time of each stimulus. The amount of depression at the point of each stimulation is equivalent to the amount of depression of the subsequent EPSC.

(C) EPSC amplitude (percentage of the first EPSC) during a train of five stimuli at 100 Hz for control conditions (black) and in the absence of the rapid component (blue).

(D) Summation of the depression waveform at 33 Hz (black, control; blue, in the absence of the rapid component). Arrows indicate the time of each stimulus.

(E) EPSC amplitude (percentage of the first EPSC) during 33 Hz train (black, control; blue, in the absence of the rapid component).

(F) Depression of fifth EPSC in the train plotted versus frequency of stimulation for control (black) and in the absence of the rapid component (blue).

has a strong temperature dependence (van der Kloot and Molgo, 1994). The experiments described so far were performed at room temperature; therefore, we performed an additional series of experiments at close to physiological temperature (34.5°C ± 0.2°C) and tested whether the presynaptic kainate receptor was activated during repetitive synaptic activation under these conditions. We also extended our analysis to frequencies of up to 200 Hz, since, at this temperature, individual EPSCs could be resolved at these very high frequencies. Similar to room temperature recordings, EPSC amplitude depressed during trains, and this depression was uniform over the entire frequency range tested (10–200 Hz; Figures 6A and 6D). LY382884 (10 μM) had no effect on the short-term depression at 10, 20, 33, or 50 Hz (Figures 6C and 6D); however, it blocked the depression at ≥100 Hz (Figures 6B and 6D). Thus, the presynaptic inhibitory kainate receptor is activated by synaptically released glutamate at physiological temperatures at frequencies >50 Hz. These data are qualitatively similar to that obtained at room temperature except in that the autoreceptor does not regulate transmission at 50 Hz. This difference is most likely due to the presynaptic kainate receptor-mediated inhibition having more rapid kinetics at the higher temperature, so that its effects have fully decayed by the time the next stimulus occurs at 50 Hz.

Developmental Regulation of the Presynaptic Kainate Receptor

Kainate receptor subunit expression is developmentally regulated in sensory thalamus and cortex (Bahn et al., 1994), and previous work has shown that postsynaptic kainate receptor function declines during the first postnatal week at thalamocortical synapses (Kidd and Isaac, 1999). Therefore, we investigated whether the regulation of thalamocortical synapses by the presynaptic kainate receptor also exhibits a developmental profile. There was no developmental change in the depression for the trains at 10, 20, or 33 Hz during the first postnatal week (Figures 7A and 7C). In contrast, however, the amount of depression caused by the 50 and 100 Hz trains decreased after P5 (Figures 7B and 7C), such that by P7–P8, there was no depression in amplitude during a 100 Hz train.

This suggests that there is a developmental loss of

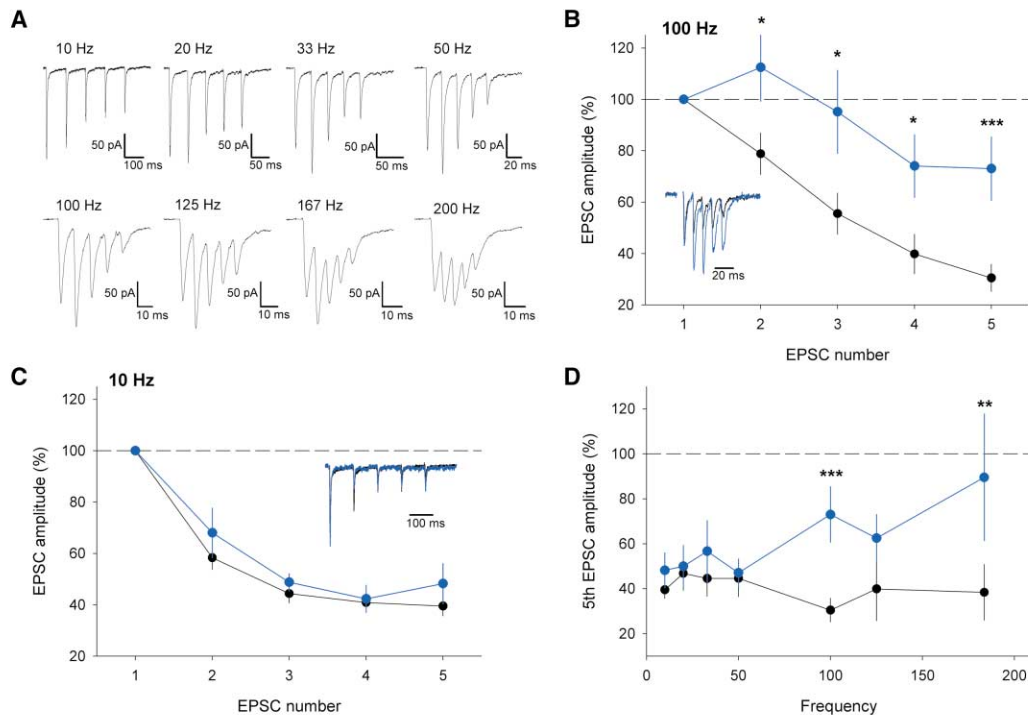

Figure 6. The Presynaptic Kainate Receptor Is Activated by Synaptically Released Glutamate at Close to Physiological Temperature

(A) Responses to trains of five stimuli at 10–200 Hz from an example control experiment at 34°C.

(B) Summary data showing EPSC amplitude (normalized to amplitude of the first EPSC in the train) during 100 Hz trains for control (black; n = 11) and in the presence of LY382884 (10 μM, blue; n = 10; *p < 0.05, ***p < 0.005) at 34.5°C. Inset shows traces (scaled to the peak of the first EPSC) from an example experiment before (black) and during (blue) the application of LY382884.

(C) Summary data for the effects of LY382884 on the response to 10 Hz trains at 34°C (n = 16 control; n = 7 in presence of LY382884).

(D) Summary data for fifth EPSC amplitude in the train (normalized to the first EPSC amplitude) as a function of train frequency for control (black; data for 167 and 200 Hz pooled; 20 Hz, n = 10; 33 Hz, n = 10; 50 Hz, n = 13; 125 Hz, n = 7; 167–200 Hz, n = 16) and in the presence of LY382884 (blue; 20 Hz, n = 7; 33 Hz, n = 7; 50 Hz, n = 7; 125 Hz, n = 6; 167–200 Hz, n = 10; **p < 0.01; ***p < 0.005).

the functional presynaptic kainate receptor at thalamocortical synapses during the first postnatal week. To test this, we investigated the sensitivity of synaptic transmission to pharmacological activation of the presynaptic kainate receptor during development. Consistent with a developmental loss of the presynaptic kainate receptor, the sensitivity of EPSCs (evoked by single-shock stimulation) to ATPA (1 μM) decreased between P5 and P8, and ATPA no longer caused a depression in EPSC amplitude by P7–P8 (Figure 7D). Thus, the sensitivity to ATPA exhibited a very similar developmental profile to the loss of the synaptic depression at 100 Hz.

Discussion

Here, we have shown that a presynaptic kainate receptor at developing thalamocortical synapses depresses transmission during brief high-frequency (50–200 Hz) trains of activity. At lower frequencies (10–33 Hz), thalamocortical synapses also exhibit depression, but this is due to a different mechanism. The kainate receptor-mediated depression at high frequencies is developmentally regulated such that it is no longer evident by the end of the first postnatal week. Thus, early in the first postnatal week, transmission at thalamocortical inputs depresses uniformly across a range of frequencies. By the end of the first postnatal week, which corresponds with the end of the critical period for these synapses (Fox, 1995), depression is absent for brief trains of activity at high frequencies (e.g., 100 Hz), but is unaffected at lower frequencies (10, 20, and 33 Hz).

We present evidence that a kainate receptor located presynaptically at thalamocortical synapses is activated over a specific frequency range by synaptically released glutamate. We have good evidence that the kainate receptor is located at a presynaptic, rather than postsynaptic, locus for a number of reasons. (1) The selective kainate receptor agonist ATPA causes a depression in EPSC amplitude that is associated with an equal change in both the AMPA and kainate receptor-mediated components of the EPSC. (2) ATPA produces no conductance change in the postsynaptic neuron. (3) ATPA causes a change in short-term plasticity, consistent with a change in presynaptic function and inconsistent with a change in postsynaptic function. (4) The kainate receptor antagonist LY382884 causes a small depression in single stimulus-evoked EPSC peak amplitude, yet it prevents depression during ≥50 Hz train stimulation. Furthermore, a direct postsynaptic inhibitory action of kainate receptors on AMPA receptors is very unlikely because we have previously demonstrated that these two receptor subtypes never colocalize at the same thalamocortical synapses during this developmental pe-

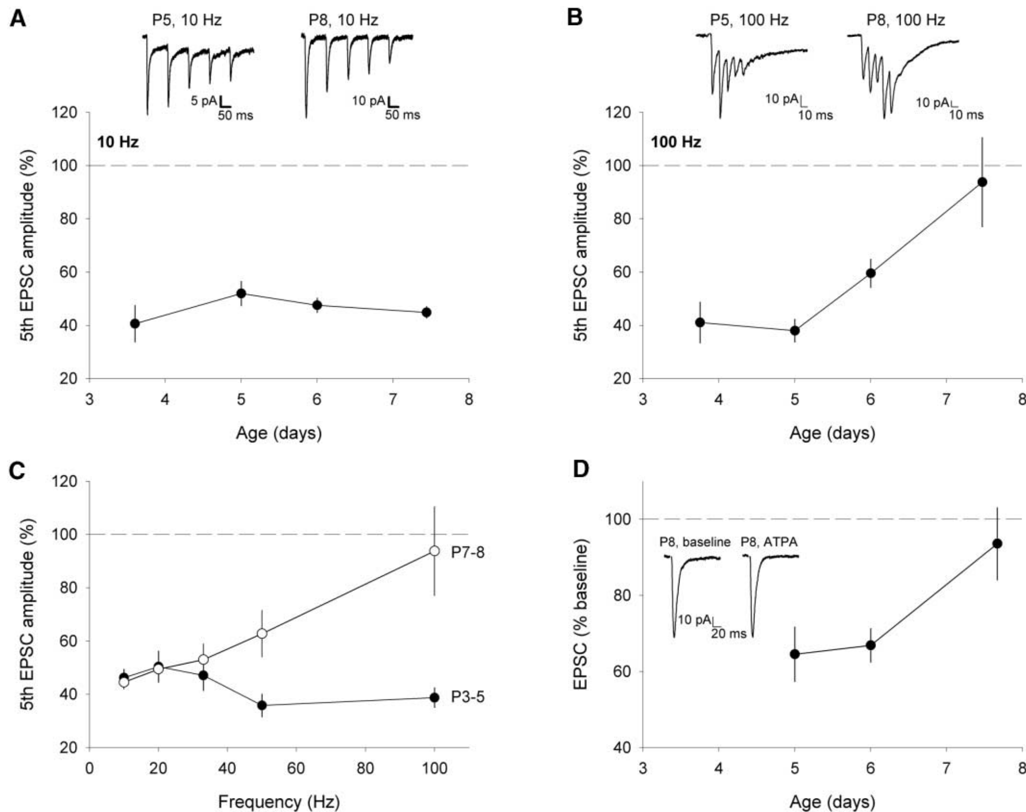

Figure 7. Developmental Regulation of the Presynaptic Kainate Receptor

(A) Summary data for the fifth EPSC amplitude (percentage of the first EPSC in the train) versus age for 10 Hz trains (P3 and 4 data pooled and P7 and 8 data pooled; P3–P4, n= 5; P5, n = 18; P6, n = 25; and P7–P8, n = 5; depression not correlated with age, p = 0.2, n = 66). Inset: examples of responses to trains of stimuli at 10 Hz for P5 and P8.

(B) Fifth EPSC amplitude (percentage of the first EPSC in the train) versus age for 100 Hz trains (data pooled from both P3 and P4 and P7 and P8. P3–P4, n = 8; P5, n = 25; P6, n = 25; and P7–P8, n = 14; amount of depression significantly correlated with age, $p < 5 \times 10^{-7}$, n = 72). Inset: examples of responses to trains of stimuli at 100 Hz for P5 and P8.

(C) Summary data for amplitude of the fifth EPSC versus frequency for P7–P8 (open symbols) and P3–P5 (closed symbols).

(D) Summary data of the effects of ATPA (1 μM) on EPSC amplitude (low-frequency stimulation; percentage of baseline) as a function of age (P5, n = 8; P6, n = 11; and P7–P8, n = 6; EPSC amplitude significantly correlated with age, $p < 0.005$, n = 25). Inset: EPSCs (averages of ten consecutive responses) from an example experiment at P8.

riod (Kidd and Isaac, 1999). One other hypothetical possibility is that activation of a postsynaptic kainate receptor causes the release of a retrograde neuromodulator that is responsible for the presynaptic effects. This neuromodulator would have to be very rapidly released for its effects to be observed during 100 Hz stimulation (i.e., within 10 ms) and seems unlikely because no postsynaptic effect of the kainate receptor agonist ATPA was observed.

Properties of Presynaptic Kainate Receptors

Presynaptic kainate receptors have been shown to regulate both excitatory and inhibitory transmission at hippocampal synapses (Kullmann, 2001; Lerma et al., 2001; Schmitz et al., 2001b) and at pathways elsewhere in the brain (Lerma et al., 2001). At inhibitory synapses, pharmacological activation of kainate receptors either inhibits or facilitates transmission in a pathway-specific and agonist concentration-dependent manner (Kullmann, 2001; Lerma et al., 2001). A number of recent studies have reported the activation of these receptors by synaptically released glutamate (Cossart et al., 2001; Jiang et al., 2001; Kerchner et al., 2001; Semyanov and Kullmann, 2001) and suggest that the physiological role of presynaptic kainate receptors in regulating GABAergic transmission can be inhibitory or facilitatory, depending on the pathway studied. There is, however, controversy surrounding the mechanism(s) by which the presynaptic kainate receptors exert these effects, since evidence has been presented for them regulating GABAergic transmission by direct depolarization of the presynaptic cell body, regulation of axonal excitability, and direct regulation of transmitter release at the terminal. In addition, a role for indirect mechanisms, such as $GABA_B$ receptors and postsynaptic shunting due to $GABA_A$ receptor activation, has also been proposed. Furthermore, there is evidence for both ionotropic and metabotropic transduction mechanisms for presynaptic kainate receptors regulating inhibitory transmission. Thus, even in the hippocampus where this has been most extensively studied, it is not clear what the overall effects of presynaptic kainate receptor activation are for the inhibitory network.

Controversy also surrounds the properties of presyn-

aptic kainate receptors regulating glutamatergic synapses (Kullmann, 2001; Lerma et al., 2001; Schmitz et al., 2001b). Pharmacological activation provides evidence for both inhibitory and facilitatory roles of presynaptic kainate receptors, multiple mechanisms of regulation, and the coupling of kainate receptors to metabotropic (as well as ionotropic) signaling pathways. So far, however, the only description of a synaptically activated kainate autoreceptor is that of the facilitatory autoreceptor regulating mossy fiber-CA3 synapses (Lauri et al., 2001a; Schmitz et al., 2001a). In the present study, we now describe a kainate autoreceptor that inhibits glutamate release.

Our data indicate that the presynaptic kainate receptor at thalamocortical inputs is rapidly activated by synaptically released glutamate (within 5 ms) and has a short-lasting effect on transmission. The result of this is that the effect of receptor activation is only evident at frequencies ≥50 Hz and is greater the higher the frequency tested (up to 200 Hz at close to physiological temperatures). This time course is consistent with an ionotropic mechanism mediated by a low-affinity receptor. At mossy fiber-CA3 synapses (Lauri et al., 2001a; Schmitz et al., 2001a), the presynaptic kainate receptor is similarly fast acting and, hence, is also thought to act via an ionotropic mechanism. However, there are important differences between the physiological functions of presynaptic kainate receptors regulating thalamocortical and mossy fiber synapses. First, at mossy fibers, the effect of the synaptic activation of the kainate receptor is much longer lasting than that observed in the present study, suggesting that the receptor at mossy fiber terminals is of higher affinity or couples to long-lasting effector mechanisms. Second, the physiological activation of the presynaptic receptor at mossy fibers produces facilitation, while that at thalamocortical terminals produces depression. It has been proposed that the kainate receptor at mossy fiber terminals produces the facilitation of transmission by increasing presynaptic Ca^{2+} entry, either by prolonging the action potential or by the channel itself being Ca^{2+} permeable (Schmitz et al., 2001a; Geiger and Jonas, 2000). However, the kainate receptor at mossy fiber terminals can produce depression when it is activated pharmacologically (Vignes et al., 1998; Bortolotto et al., 1999; Contractor et al., 2000; Kamiya and Ozawa, 2000; Schmitz et al., 2000, 2001a; Lauri et al., 2001a) or heterosynaptically (Schmitz et al., 2000), and this is mimicked when mossy fibers are strongly depolarized by raising the extracellular K^+ concentration (Schmitz et al., 2001a).

One possibility to explain the inhibition of release by the presynaptic kainate receptor at thalamocortical terminals is that it reduces the influx of Ca^{2+} associated with the action potential. This could be due to the receptor generating sufficient depolarization at the terminal to inactivate presynaptic voltage-gated Ca^{2+} channels and/or significantly reduce the driving force for Ca^{2+}. The difference between mossy fiber-CA3 and thalamocortical synapses in terms of the physiological effect of presynaptic kainate receptor activation may reflect differences in the morphology of these two types of terminals. The depolarization produced by the current flowing through the receptor at the smaller thalamocortical terminals may produce a relatively large depolarization sufficient to cause the reduction in Ca^{2+} influx. However, in the larger mossy fiber terminals, the same amount of current may only produce a limited depolarization sufficient to facilitate release.

Mechanism for Depression at 10–33 Hz

The time course of the depression at 10, 20, and 33 Hz is consistent with a receptor-activated G protein-mediated depression of release, as indicated by the modeling. One well-characterized inhibitory presynaptic metabotropic receptor at glutamatergic synapses is the presynaptic mGluR at mossy fiber-CA3 synapses (Scanziani et al., 1997). However, in the present study, broad-spectrum mGluR antagonists did not affect short-term depression at thalamocortical synapses, providing evidence against this mechanism. Another possible mechanism is regulation of transmission by a heteroreceptor. $GABA_B$ receptors have been shown to regulate glutamatergic transmission at CA1 synapses in the hippocampus (Davies et al., 1993; Isaacson et al., 1993) and have been reported to mediate some of the effects of ATPA at the mossy fiber-CA3 synapse (Schmitz et al., 2000; but see Lauri et al., 2001b). However, $GABA_B$ receptors have been shown not to regulate transmission at thalamocortical synapses (Gil et al., 1997), and in the present study, a $GABA_B$ receptor antagonist did not block the effects of ATPA. Other possible presynaptic receptor mechanisms include regulation via muscarinic acetylcholine receptors (Gil et al., 1997), 5-HT receptors (Lebrand et al., 1996), or a kainate receptor not blocked by 10 μM LY382884.

Role of Short-Term Plasticity at Developing Thalamocortical Synapses

This frequency-dependent distinction between the mechanisms regulating thalamocortical synapses is of interest because it correlates with the two physiologically important bands of frequencies of activity observed in vivo in VPM neurons. This has been most extensively documented in adult rats where the low frequencies (≤33 Hz) correspond to activity in the absence of sensory stimulation, and the high frequencies (≥50 Hz) correspond to activity observed when the whiskers are stimulated (e.g., Nicolelis and Chapin, 1994). There are no in vivo studies in which the firing patterns of VPM neurons in neonates were recorded; however, there is one study that reports the firing properties of neurons in S1 barrel cortex in P6 anesthetised rats (Armstrong-James, 1975), and this suggests that VPM neurons in neonates can fire at ~100 Hz. In support of this, we also show in the present study that at physiological temperatures, thalamocortical axons can support action potentials at frequencies of up to 200 Hz. The depression observed at these high frequencies is blocked by the kainate receptor antagonist, indicating that it is not due to axon fatigue or refractoriness but, rather, the activation of the inhibitory presynaptic kainate receptor. All of this suggests that in the neonate, the presynaptic kainate receptor could be activated by sensory-evoked activity.

The importance of the dynamic properties of synapses for information processing in cortical networks has only recently been considered (Abbott et al., 1997; Tsodyks and Markram, 1997; Markram et al., 1998). Short-term depression is a common feature of many

intracortical (Thomson and Deuchars, 1994; Stratford et al., 1996; Abbott et al., 1997; Tsodyks and Markram, 1997; Markram et al., 1998) and thalamocortical (Finnerty et al., 1999; Finnerty and Connors, 2000; Gil et al., 1997, 1999; Stratford et al., 1996; Castro-Alamancos and Connors, 1997) synapses. There is evidence that such activity-dependent, short-term depression enables the signaling of changes in the firing rate of presynaptic neurons, independently of the absolute firing rate (Abbott et al., 1997; Tsodyks and Markram, 1997; Markram et al., 1998). Synapses that do not exhibit depression are thought to transfer information about the absolute firing rate of presynaptic neurons and, under these conditions, high-frequency inputs dominate in determining the postsynaptic response of neurons (Abbott et al., 1997). Therefore, nondepressing inputs are likely to drive the postsynaptic cell, while depressing inputs may perform a more modulatory role.

Here, we have shown that early in development the immature thalamocortical input uniformly exhibits depression at all frequencies examined. The presynaptic kainate receptor specifically causes depression at high frequencies (≥50 Hz), and it is these frequencies that are associated with activation of the whiskers in the mature system. By the end of the first postnatal week, the presynaptic kainate receptor mechanism is lost. This enables thalamocortical synapses to exhibit either depression or no depression, depending on the frequency. This suggests that by the end of the first postnatal week, thalamocortical synapses exhibit the property that they signal different types of information depending on the frequency of activity of the presynaptic neurons. During whisker activation, thalamocortical synapses would provide information about the absolute presynaptic firing rate and drive layer IV neurons. However, in the absence of such activity, thalamocortical synapses may be modulatory due to the short-term depression. Our data indicate that an important mechanism for producing these dynamic properties of thalamocortical synapses is the developmental down-regulation of the presynaptic kainate receptor. This allows thalamocortical synapses to selectively transfer high-frequency activity to the cortex and, thus, may set up the system to process high-frequency, sensory-evoked activity.

The thalamocortical input to layer IV is considered to be "driving" rather than "modulating" (Crick and Koch, 1998; Sherman and Guillery, 1998). However, our data suggest that these synapses may actually function in both ways depending upon the frequency of presynaptic activity. That is, whether an input is a "driver" or a "modulator" may be dependent not only upon the input's "absolute" synaptic strength (Tsodyks and Markram, 1997; Crick and Koch, 1998; Markram et al., 1998; Sherman and Guillery, 1998), but also on the frequency at which it is activated. Importantly, in this scheme, the thalamocortical input would be driving only during sensory-evoked activity. The dynamic properties of thalamocortical synapses may therefore be highly significant for the effective signaling of sensory information to the cortex, and the developmental loss of the presynaptic kainate receptor may be an important step in the maturation of the sensory-processing network.

Experimental Procedures

Electrophysiology

Thalamocortical slices (500 μm) were prepared from rat pups (P3–P8; P0 is the day of birth) and whole-cell voltage-clamp recordings (3–6 MΩ electrodes, −70 mV holding potential) were made from layer IV neurons in the somatosensory barrel cortex, as previously described (Feldman et al., 1998; Kidd and Isaac, 1999). The extracellular solution was as follows: 119 mM NaCl, 2.5 mM KCl, 1.0 mM NaH_2PO_4, 26.2 mM $NaHCO_3$, 2.5 mM $CaCl_2$, 1.3 mM $MgSO_4$, and 11 mM glucose and was saturated with 95% O_2/5% CO_2. The majority of recordings were performed at room temperature (23°C–25°C); however, in some experiments, recordings were performed at close to physiological temperature (34.5°C ± 0.2°C, range = 33°C–36°C, n = 9 cells), and bath temperature was continuously monitored during experiments by a thermister located in the recording chamber. D-AP5 (100 μM) and picrotoxin (50 μM) were included in the extracellular solution to block NMDA and $GABA_A$ receptors, respectively. The intracellular solution was as follows: 135 mM $CsMeSO_4$, 8 mM NaCl, 10 mM Hepes, 0.5 mM EGTA, 4 mM Mg-ATP, and 0.3 mM Na-GTP (pH 7.25). The osmolarity was 285 mOsm. In some experiments, QX-314 (5 mM) was also included. EPSCs at thalamocortical synapses were evoked by electrical stimulation of ventrobasal thalamus or the white matter, as previously described (Agmon and Connors, 1991; Feldman et al., 1998; Kidd and Isaac, 1999). In some cells, data from two pathways were collected. Recordings were made using an Axopatch 200-B amplifier, filtered at 5 KHz, and digitized at 10 KHz. On-line analysis of EPSC amplitude, series resistance, and input resistance was performed using the LTP program (Anderson and Collingridge, 2001). Series resistance was monitored on-line and estimated as previously described (Kidd and Isaac, 1999).

Analysis

The responses to train stimulation were determined by averaging between 9 and 15 trials for each frequency. The variability in the response to train stimulation was low, such that the use of this number of trials produced standard errors of ∼5% of the mean peak EPSC amplitude values. For estimation of peak amplitude of each EPSC during a train, postsynaptic summation was removed (Kidd and Isaac, 2001). This was performed as follows: the mean EPSC (average of ten) evoked by single-shock stimulation (collected immediately before the train) was used as a template ($EPSC_{single}$). The $EPSC_{single}$ was then scaled to the peak of the first EPSC in the response to the train ($EPSC_{train}$) and subtracted from $EPSC_{train}$. This produced an $EPSC_{train}$ comprising four EPSCs. The peak amplitude of the first of the remaining EPSCs was measured (equal to the peak amplitude of the second EPSC in the train in the absence of postsynaptic summation). $EPSC_{single}$ was then scaled to the peak of the first EPSC of the four remaining EPSCs in $EPSC_{train}$ and subtracted from $EPSC_{train}$. This produced an $EPSC_{train}$ comprised of three remaining EPSCs. The peak amplitude of the first of the remaining EPSCs was then measured (equal to the peak amplitude of the third EPSC in the train in the absence of postsynaptic summation). This process was repeated sequentially until the summation was removed for all the remaining EPSCs in the train. For this analysis, all steps of the subtraction procedure were monitored visually to ensure that no errors occurred during subtraction. We have previously shown that the AMPA and kainate receptor-mediated components to thalamocortical EPSCs sum linearly during repetitive stimulation (Kidd and Isaac, 2001).

For analysis of the charge associated with the AMPA receptor and kainate receptor-mediated components of the EPSC, the decay of the EPSC was fitted with the sum of two exponentials (a best fit was obtained by iteratively fitting the decay using SigmaPlot 5.0; Kidd and Isaac 1999). The charge for each component is the product of τ and the current at the peak (t = 0). Previously, we have shown pharmacologically that the slow exponential component of the decay of the EPSC corresponds to the kainate receptor-mediated component and the estimate of the kinetics associated with this component is not affected by the fast AMPA receptor-mediated component (Kidd and Isaac 1999, 2001).

Modeling

Data for the depression during trains of five EPSCs at 10, 20, 33, 50, and 100 Hz at room temperature were modeled. The model uses a waveform describing the depression of release following a single synaptic activation (the depression waveform). The depression waveform was constructed from two components: (1) a fast component with a peak inhibition of release (C_{fast}), immediately following synaptic activation, decaying exponentially with a single time constant (τ_{fast}), and (2) a delayed slow component with a latency to onset of 20 ms, rising with a single exponential (C_{rise}, τ_{rise}) and decaying biexponentially (C_{slow1}, τ_{slow1}; C_{slow2}, τ_{slow2}; see Figure 5A). The form of these two components was chosen as a best guess based on the reported properties for a rapidly acting kainate autoreceptor at mossy fiber-CA3 synapses (for the fast component; Lauri et al., 2001a; Schmitz et al., 2001a) and for the $GABA_B$ receptor-mediated inhibition of glutamatergic synapses in the hippocampus (for the slow component; Davies and Collingridge, 1996). This model was chosen because it describes well the data from the previous studies and also the experimental data in the present study. However, this may not be an exclusive model to describe the data.

To calculate the depression during trains of five stimuli, the depression waveform was summed linearly (Figures 5B and 5D) and percent inhibition of the EPSC relative to the first EPSC in the train computed at the time of each stimulus. The best solution for the model (providing the smallest squared difference from the experimental data) was found by iterating the parameters of the depression waveform using Microsoft Excel Solver (Microsoft Excel 2000). All the kinetic parameters of the depression waveform were allowed to vary; however, the overall form of the depression waveform was constrained to the two components of depression described above.

Statistical Analysis

Data are expressed as mean ± SEM. The number of observations represents the number of pathways, unless otherwise stated. Statistical analyses were performed both on data for individual pathways and on data from individual cells (for this latter analysis, any data obtained from two pathways onto the same cell were averaged to produce a single value). For both analyses, the same experimental manipulations achieved statistical significance. Statistical analysis and data are presented using the analysis of pathways. Statistical significance was assessed using the Student's t test. ATPA, D-AP5, LY341495, MCPG, and CCPG were purchased from Tocris Cookson. CGP55845A was a gift from Novartis, but it is also available commercially from Tocris Cookson. LY382884 was a gift from Eli Lilly and Co., but it can be synthesized according to the published method (Bleisch et al., 1997).

Acknowledgments

We are grateful to David Lodge at Eli Lilly and Co. for the gift of LY382884 and to Mario Pozza at Novartis for providing CGP55845A. We are grateful to Dr. W. Anderson for supplying the LTP program. This work was supported by the MRC (G.L.C. and J.T.R.I.) and the Wellcome Trust (G.L.C., J.W.C., and J.T.R.I.).

Received: September 17, 2001
Revised: April 12, 2002

References

Abbott, L.F., Varela, J.A., Sen, K., and Nelson, S.B. (1997). Synaptic depression and cortical gain control. Science *275*, 220–224.

Agmon, A., and Connors, B.W. (1991). Thalamocortical responses of mouse somatosensory (barrel) cortex in vitro. Neuroscience *41*, 365–379.

Anderson, W.W., and Collingridge, G.L. (2001). The LTP program: a data acquisition program for on-line analysis of long-term potentiation and other synaptic events. J. Neurosci. Methods *108*, 71–83.

Armstrong-James, M. (1975). The functional status and columnar organization of single cells responding to cutaneous stimulation in neonatal rat somatosensory cortex S1. J. Physiol. (Lond.) *246*, 501–538.

Bahn, S., Volk, B., and Wisden, W. (1994). Kainate receptor gene expression in the developing rat brain. J. Neurosci. *14*, 5525–5547.

Bettler, B., and Mulle, C. (1995). Neurotransmitter receptors II. AMPA and kainate receptors. Neuropharmacology *34*, 123–139.

Bleisch, T.J., Ornstein, P.L., Allen, N.K., Wright, R.A., Lodge, D., and Schoepp, D.D. (1997). Structure activity studies of aryl-spaced decahydroisoquinoline-3-carboxylic acid AMPA receptor antagonists. Bioorg. Med. Chem. Lett. *7*, 1161–1166.

Bortolotto, Z.A., Clarke, V.R.J., Delany, C.M., Parry, M.C., Smolders, I., Vignes, M., Ho, K.H., Miu, P., Brinton, B.T., Fantaske, R., et al. (1999). Kainate receptors are involved in synaptic plasticity. Nature *402*, 297–301.

Castro-Alamancos, M.A., and Connors, B.W. (1997). Thalamocortical synapses. Prog. Neurobiol. *51*, 581–606.

Chittajallu, R., Vignes, M., Dev, K.K., Barnes, J.M., Collingridge, G.L., and Henley, J.M. (1996). Regulation of glutamate release by presynaptic kainate receptors in the hippocampus. Nature *379*, 78–81.

Clarke, V.R., Ballyk, B.A., Hoo, K.H., Mandelzys, A., Pellizzari, A., Bath, C.P., Thomas, J., Sharpe, E.F., Davies, C.H., Ornstein, P.L., et al. (1997). A hippocampal GluR5 kainate receptor regulating inhibitory synaptic transmission. Nature *389*, 599–603.

Contractor, A., Swanson, G.T., Sailer, A., O'Gorman, S., and Heinemann, S.F. (2000). Identification of the kainate receptor subunits underlying modulation of excitatory synaptic transmission in the CA3 region of the hippocampus. J. Neurosci. *20*, 8269–8278.

Contractor, A., Swanson, G.T., and Heinemann, S.F. (2001). Kainate receptors are involved in short- and long-term plasticity at mossy fiber synapses in the hippocampus. Neuron *29*, 209–216.

Cossart, R., Esclapez, M., Hirsch, J.C., Bernard, C., and Ben-Ari, Y. (1998). GluR5 kainate receptor activation in interneurons increases tonic inhibition of pyramidal cells. Nat. Neurosci. *1*, 470–478.

Cossart, R., Tyzio, R., Dinocourt, C., Esclapez, M., Hirsch, J.C., Ben-Ari, Y., and Bernard, C. (2001). Presynaptic kainate receptors that enhance the release of GABA on CA1 hippocampal interneurons. Neuron *29*, 497–508.

Crair, M.C., and Malenka, R.C. (1995). A critical period for long-term potentiation at thalamocortical synapses. Nature *375*, 325–328.

Crick, F., and Koch, C. (1998). Constraints on cortical and thalamic projections: the no-strong-loops hypothesis. Nature *391*, 245–250.

Davies, C.H., and Collingridge, G.L. (1996). Regulation of EPSPs by the synaptic activation of $GABA_B$ autoreceptors in rat hippocampus. J. Physiol. (Lond.) *496*, 451–470.

Davies, C.H., Pozza, M.F., and Collingridge, G.L. (1993). CGP 55845A: a potent antagonist of $GABA_B$ receptors in the CA1 region of rat hippocampus. Neuropharmacology *32*, 1071–1073.

Feldman, D.E., Nicoll, R.A., Malenka, R.C., and Isaac, J.T.R. (1998). Long-term depression at thalamocortical synapses in developing rat somatosensory cortex. Neuron *21*, 347–357.

Finnerty, G.T., and Connors, B.W. (2000). Sensory deprivation without competition yields modest alterations of short-term synaptic dynamics. Proc. Natl. Acad. Sci. USA *97*, 12864–12868.

Finnerty, G.T., Roberts, L.S.E., and Connors, B.W. (1999). Sensory experience modifies the short-term dynamics of neocortical synapses. Nature *400*, 367–371.

Fox, K. (1995). The critical period for long-term potentiation in primary sensory cortex. Neuron *15*, 485–488.

Frerking, M., Schmitz, D., Zhou, Q., Johansen, J., and Nicoll, R.A. (2001). Kainate receptors depress excitatory synaptic transmission at CA3→CA1 synapses in the hippocampus via a direct presynaptic action. J. Neurosci. *21*, 2958–2966.

Geiger, J.R., and Jonas, P. (2000). Dynamic control of presynaptic Ca^{2+} inflow by fast-inactivating K^+ channels in hippocampal mossy fiber boutons. Neuron *28*, 927–939.

Gil, Z., Connors, B.W., and Amitai, Y. (1997). Differential regulation of neocortical synapses by neuromodulators and activity. Neuron *19*, 679–686.

Gil, Z., Connors, B.W., and Amitai, Y. (1999). Efficacy of thalamocorti-

cal and intracortical synaptic connections: quanta, innervation, and reliability. Neuron *23*, 385–397.

Isaacson, J.S., Solis, J.M., and Nicoll, R.A. (1993). Local and diffuse synaptic actions of GABA in the hippocampus. Neuron *10*, 165–175.

Jiang, L., Xu, J., Nedergaard, M., and Kang, J. (2001). A kainate receptor increases the efficacy of GABAergic synapses. Neuron *30*, 503–513.

Kamiya, H., and Ozawa, S. (1998). Kainate receptor-mediated inhibition of presynaptic Ca^{2+} influx and EPSP in area CA1 of the rat hippocampus. J. Physiol. (Lond.) *509*, 833–845.

Kamiya, H., and Ozawa, S. (2000). Kainate receptor-mediated presynaptic inhibition at the mouse hippocampal mossy fibre synapse. J. Physiol. (Lond.) *523*, 653–665.

Kerchner, G.A., Wang, G.D., Qiu, C.S., Huettner, J.E., and Zhuo, M. (2001). Direct presynaptic regulation of GABA/glycine release by kainate receptors in the dorsal horn: an ionotropic mechanism. Neuron *32*, 477–488.

Kidd, F.L., and Isaac, J.T.R. (1999). Developmental and activity-dependent regulation of kainate receptors at thalamocortical synapses. Nature *400*, 569–573.

Kidd, F.L., and Isaac, J.T.R. (2001). Kinetics and activation of postsynaptic kainate receptors at thalamocortical synapses: role of glutamate clearance. J. Neurophysiol. *86*, 1139–1148.

Kullmann, D.M. (2001). Presynaptic kainate receptors in the hippocampus: slowly emerging from obscurity. Neuron *32*, 561–564.

Lauri, S.E., Bortolotto, Z.A., Bleakman, D., Ornstein, P.L., Lodge, D., Isaac, J.T.R., and Collingridge, G.L. (2001a). A critical role of a facilitatory kainate autoreceptor in mossy fibre LTP. Neuron *32*, 697–709.

Lauri, S.E., Delaney, C., Clarke, V., Bortolotto, Z.A., Ornstein, P.L., Isaac, J.T.R., and Collingridge, G.L. (2001b). Synaptic activation of a presynaptic kainate receptor facilitates AMPA receptor-mediated synaptic transmission at hippocampal mossy fibre synapses. Neuropharmacology *41*, 907–915.

Lebrand, C., Cases, O., Adelbrecht, C., Doye, A., Alvarez, C., El Mestikawy, S., Seif, I., and Gaspar, P. (1996). Transient uptake and storage of serotonin in developing thalamic neurons. Neuron *17*, 823–835.

Lerma, J., Paternain, A.V., Rodriguez-Moreno, A., and Lopez-Garcia, J.C. (2001). Molecular physiology of kainate receptors. Physiol. Rev. *81*, 971–998.

Markram, H., Pikus, D., Gupta, A., and Tsodyks, M. (1998). Potential for multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses. Neuropharmacology *37*, 489–500.

Nicolelis, M.A.L., and Chapin, J.K. (1994). Spatiotemporal structure of somatosensory responses of many-neuron ensembles in the rat ventral posterior medial nucleus of the thalamus. J. Neurosci. *14*, 3511–3532.

Scanziani, M., Salin, P.A., Vogt, K.E., Malenka, R.C., and Nicoll, R.A. (1997). Use-dependent increases in glutamate concentration activate presynaptic metabotropic glutamate receptors. Nature *385*, 630–634.

Schmitz, D., Frerking, M., and Nicoll, R.A. (2000). Synaptic activation of presynaptic kainate receptors on hippocampal mossy fiber synapses. Neuron *27*, 327–338.

Schmitz, D., Mellor, J., and Nicoll, R.A. (2001a). Presynaptic kainate receptor mediation of frequency facilitation at hippocampal mossy fibre synapses. Science *291*, 1972–1976.

Schmitz, D., Mellor, J., Frerking, M., and Nicoll, R.A. (2001b). Presynaptic kainate receptors at hippocampal mossy fiber synapses. Proc. Natl. Acad. Sci. USA *98*, 11003–11008.

Semyanov, A., and Kullmann, D.M. (2001). Kainate receptor-dependent axonal depolarization and action potential initiation in interneurons. Nat. Neurosci. *4*, 718–723.

Sherman, S.M., and Guillery, R.W. (1998). On the actions that one nerve cell can have on another: distinguishing "drivers" from "modulators." Proc. Natl. Acad. Sci. USA *95*, 7121–7126.

Stratford, K.J., Tarczy-Hornoch, K., Martin, K.A.C., Bannister, N.J., and Jack, J.J.B. (1996). Excitatory synaptic inputs to spiny stellate cells in cat visual cortex. Nature *382*, 258–261.

Thomas, N.K., Hawkins, L.M., Miller, J.C., Troop, H.M., Roberts, P.J., and Jane, D.E. (1998). Pharmacological differentiation of kainate receptors on neonatal rat spinal motoneurones and dorsal roots. Neuropharmacology *37*, 1223–1237.

Thomson, A.M., and Deuchars, J. (1994). Temporal and spatial properties of local circuits in neocortex. Trends Neurosci. *17*, 119–126.

Tsodyks, M., and Markram, H. (1997). The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. Proc. Natl. Acad. Sci. USA *94*, 719–723.

Van der Kloot, W., and Molgo, J. (1994). Quantal acetylcholine release at the vertebrate neuromuscular junction. Physiol. Rev. *74*, 899–991.

Vignes, M., Clarke, V.R.J., Parry, M.J., Bleakman, D., Lodge, D., Ornstein, P.L., and Collingridge, G.L. (1998). The GluR5 subtype of kainate receptors regulates excitatory synaptic transmission in areas CA1 and CA3 of the rat hippocampus. Neuropharmacology *37*, 1269–1277.