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$GABA_{A,slow}$: causes and consequences

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$GABA_A$ receptors in the CNS mediate both fast synaptic and tonic inhibition. Over the past decade a phasic current with features intermediate between fast synaptic and tonic inhibition, termed $GABA_{A,slow}$, has received increasing attention. This has coincided with an ever-growing appreciation for GABAergic cell type diversity. Compared with classical fast synaptic inhibition, $GABA_{A,slow}$ is slower by an order of magnitude. In this review, we summarize recent studies that have enhanced our understanding of $GABA_{A,slow}$. These include the discovery of specialized interneuron types from which this current originates, the factors that could underlie its characteristically slow kinetics, its contribution to specific aspects of integrative function and network oscillations, and its potential usefulness as a novel drug target for modulating inhibitory synaptic transmission in the CNS.

Introduction

γ-Aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS, activates both ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors. Classically, $GABA_A$ receptor-mediated inhibition was thought to consist exclusively of fast inhibitory postsynaptic potentials (IPSPs) mediated by low-affinity receptors activated in a transient manner by synaptically-released GABA [1,2]. Subsequently, a persistent form of receptor-mediated inhibition was recognized that is produced by GABA acting on high-affinity extrasynaptic $GABA_A$ receptors [2,3]. These two signals mediate respectively a fast phasic and a continuous tonic inhibition.

A third form of $GABA_A$ receptor-mediated inhibition, termed $GABA_{A,slow}$, has also been described [4], and recently this has received increased attention. It consists of a slowly rising and slowly decaying phasic inhibitory postsynaptic current (IPSC), with kinetics intermediate between classical $GABA_{A,fast}$ and $GABA_B$ mediated currents. $GABA_{A,slow}$ has been demonstrated in the hippocampus [4] and neocortex [5–7], and currents with slow IPSCs similar to $GABA_{A,slow}$ have been also reported in several other brain areas including the thalamus [8–10], cerebellum [11,12], amygdala [13,14] and brainstem [15]. We review here the unique characteristics of $GABA_{A,slow}$, including the cell types that generate it, the underlying spatiotemporal profile of the transmitter transient, its pharmacology, and current hypotheses about its physiological role in hippocampal circuits.

For the purposes of this review we define $GABA_{A,slow}$ as a spontaneous or evoked $GABA_A$-receptor-mediated phasic current with a decay constant of > 30 ms. We focus primarily on data obtained in the hippocampus because this is the area where it has been studied most intensively and where the distinction between fast and slow IPSCs observed in individuals neurons is the clearest. However, it should be noted that phasic IPSCs display a broad range of kinetics, some of which are intermediate between those of fast and slow IPSCs [16,17]. Direct comparison between studies is complicated by the impact on IPSC kinetics of the recording conditions – including the concentration of chloride [18], the voltage [19], and the different methods of kinetic characterization and analysis [15,20–22]. Nevertheless, consistent and clear distinctions between different kinetic classes of IPSCs indicate that fast and slow IPSCs are not simply the two ends of a single broad distribution; instead these arise from distinct classes of presynaptic neurons and their kinetics reflect substantially different biophysical mechanisms.

$GABA_{A,slow}$ in the hippocampus

$GABA_{A,slow}$ was first described as a distinct form of synaptic inhibition in hippocampal CA1 pyramidal neurons when voltage-clamp recordings revealed an IPSC with a slow decay (30–70 ms) following stimulation of dendritic layers [4]. By comparison, a stimulating electrode placed close to the stratum pyramidale elicited a response with a

Glossary

Gamma-frequency network oscillation: rhythmic neural activity with a frequency of 25–70 Hz.
High-affinity receptors: high affinity for ligand binding implies that a relatively low concentration of the ligand is adequate to maximally occupy its binding site and trigger a physiological response. Typically this is associated with a slow unbinding rate and a long-lasting conductance.
Intrinsic membrane conductances: channels that can be voltage- and/or ligand-gated and that can interact with synaptic conductances to determine the functional output of a neuron.
Low-affinity receptors: low affinity for ligand-binding implies that a relatively high concentration of the ligand is required for its binding site to be maximally occupied and for the maximum physiological response to be achieved. Typically this is associated with rapid ligand unbinding and a rapidly decaying conductance.
Spatiotemporal profile of neurotransmitter: the time-course and spatial distribution of a neurotransmitter at the synaptic cleft and/or at perisynaptic sites.
Suppression of fast inhibition (SFI): stimulation of interneurons of the SLM that evoke slow IPSCs in pyramidal cells simultaneously depresses the frequency and the amplitude of spontaneous fast IPSCs also impinging onto pyramidal cells for several hundred milliseconds.
Theta-frequency network oscillation: rhythmic neural activity with a frequency of 4–8 Hz.
Voltage-jump method: a method used to assess the time-course of synaptic conductance. A voltage step that occurs while a synaptic conductance is still active will boost the synaptic driving force to evoke additional charge flow.
Volume transmission: a mode of synaptic transmission whereby a chemical message diffuses over long distances (microns) to reach high-affinity receptors on target neurons.

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rapid decay rate (3–8 ms) that matched the decay of the majority of the abundant spontaneous IPSCs observed in pyramidal cells. Further studies revealed additional differences between $GABA_{A,fast}$ and $GABA_{A,slow}$. These include suppression of $GABA_{A,slow}$ (but not of $GABA_{A,fast}$) by dendritic application of the $GABA_A$ receptor channel blocker picrotoxin [4], differential sensitivity to the GABA transporter GAT1 antagonist NO-711 [23] and to $GABA_B$ receptor ligands [24], and different profiles of paired-pulse depression [24]. Slow spontaneous and miniature IPSCs (sIPSCs and mIPSCs) occur at low frequency compared to fast IPSCs [17,23], but their frequency is increased when the firing rate of selective presynaptic interneurons is pharmacologically enhanced [25] (Figure 1).

Which cell types mediate $GABA_{A,slow}$?

A wide variety of GABAergic interneurons are present in the forebrain. Indeed, in the hippocampal CA1 region at least 21 distinct types of interneurons have been described [26]. Distinct types of interneurons innervate specific subcellular domains of pyramidal cells, with 92% of GABAergic synapses contacting the dendritic domain of CA1 pyramidal cells [27]. Among the different types of interneurons the neurogliaform cell (NGFC) in the neocortex [7,28–30] and hippocampus [31,32], and the Ivy cell of the hippocampus [33], have been most clearly demonstrated to mediate $GABA_{A,slow}$ (Figure 2). A hallmark of NGFCs and Ivy cells is profuse axon branching that produces an unusually dense arbor [33–41]. This characteristic might be an important factor in generating $GABA_{A,slow}$.

NGFCs elicit $GABA_{A,slow}$ in all their target cells identified so far. These include other NGFCs, additional types of interneurons, the dendrites of pyramidal cells [7,28,31,32], and even themselves, through autaptic connections [42]. Therefore, a subpopulation of dendrite-targeting interneurons appears to mediate $GABA_{A,slow}$, as predicted by

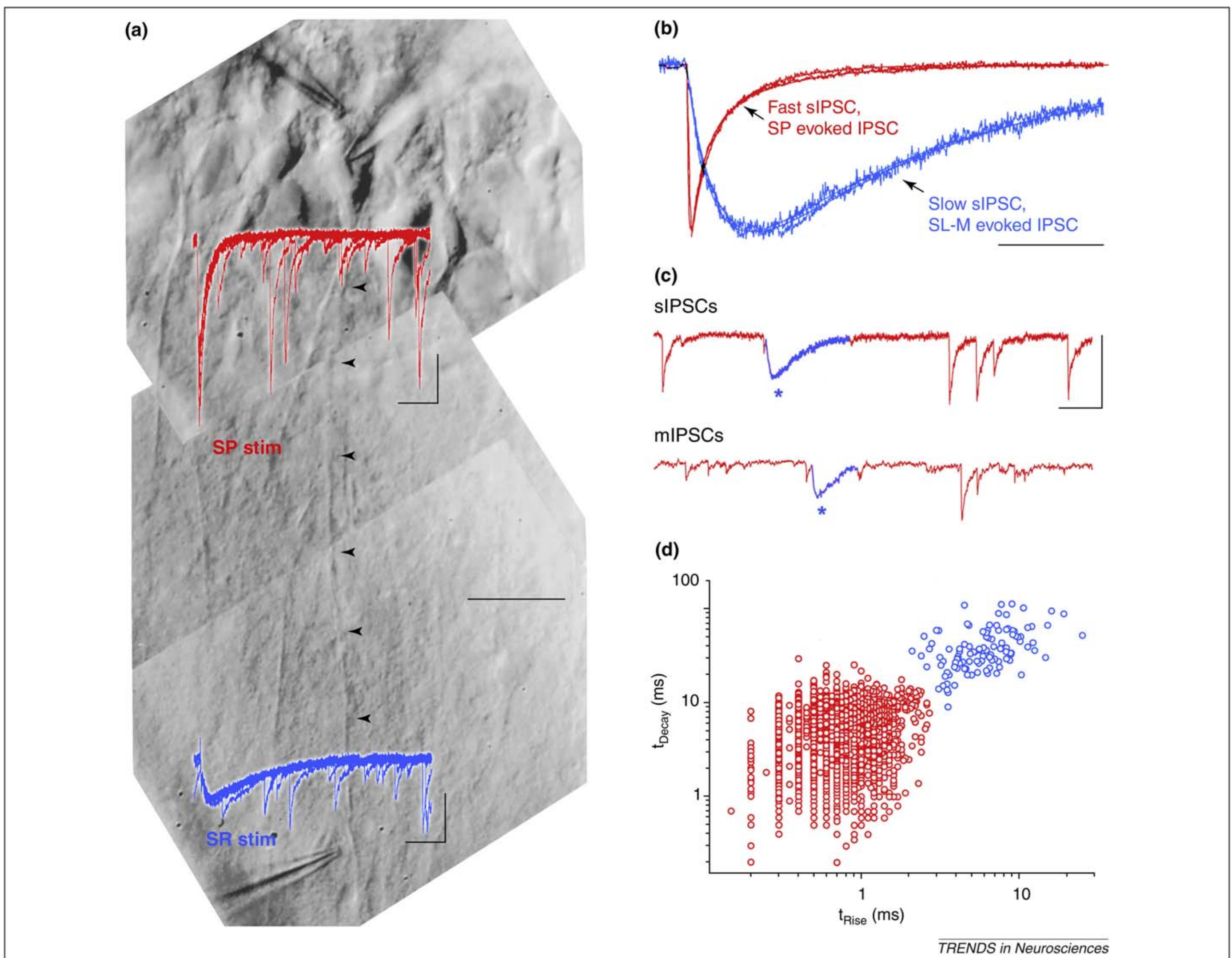

Figure 1. Evoked (evoked IPSCs), spontaneous (sIPSCs) and miniature (mIPSCs) synaptic $GABA_{A,slow}$ in the hippocampus. Evoked IPSCs are elicited by electrical stimulation, and sIPSCs and mIPSC occur spontaneously in the absence or presence of tetrodotoxin (TTX) to block action potentials, respectively. **(a)** Monosynaptic IPSCs evoked by stimuli (stim) in stratum pyramidale (SP) and radiatum (SR) recorded in the CA1 pyramidal cell illustrated in the photomicrograph (scale bar, 20 μm). The stimulating glass electrodes can be seen entering the field of view from the top- and the bottom-left of the photomicrograph. In the traces, from the left, evoked IPSCs are illustrated followed by overlying fast sIPSCs. Scale bars, 100 pA, 50 ms. **(b)** Averaged and normalized fast sIPSCs, SP-evoked IPSCs, slow sIPSCs, and SLM-evoked IPSCs recorded in a CA1 pyramidal cell. Best fits to exponential functions are also shown. Scale bar, 25 ms. **(c)** Kinetic heterogeneity of sIPSCs and mIPSCs recorded from CA1 pyramidal cells. Slow sIPSCs and mIPSCs are highlighted (blue portion of the traces and asterisks). Calibration bars, 200 pA, 100 ms. **(d)** A scatterplot of the decay time (t_{Decay}) versus the rise time (t_{Rise}) is shown for >5000 sIPSCs recorded in CA1 pyramidal cells. Most of the sIPSCs have fast kinetics and are clustered in the lower left quadrant of the plot (red circles), whereas a few display slower kinetics (blue circles) and are proposed to correspond to $GABA_{A,\ slow}$. All panels adapted, with permission, from [23].

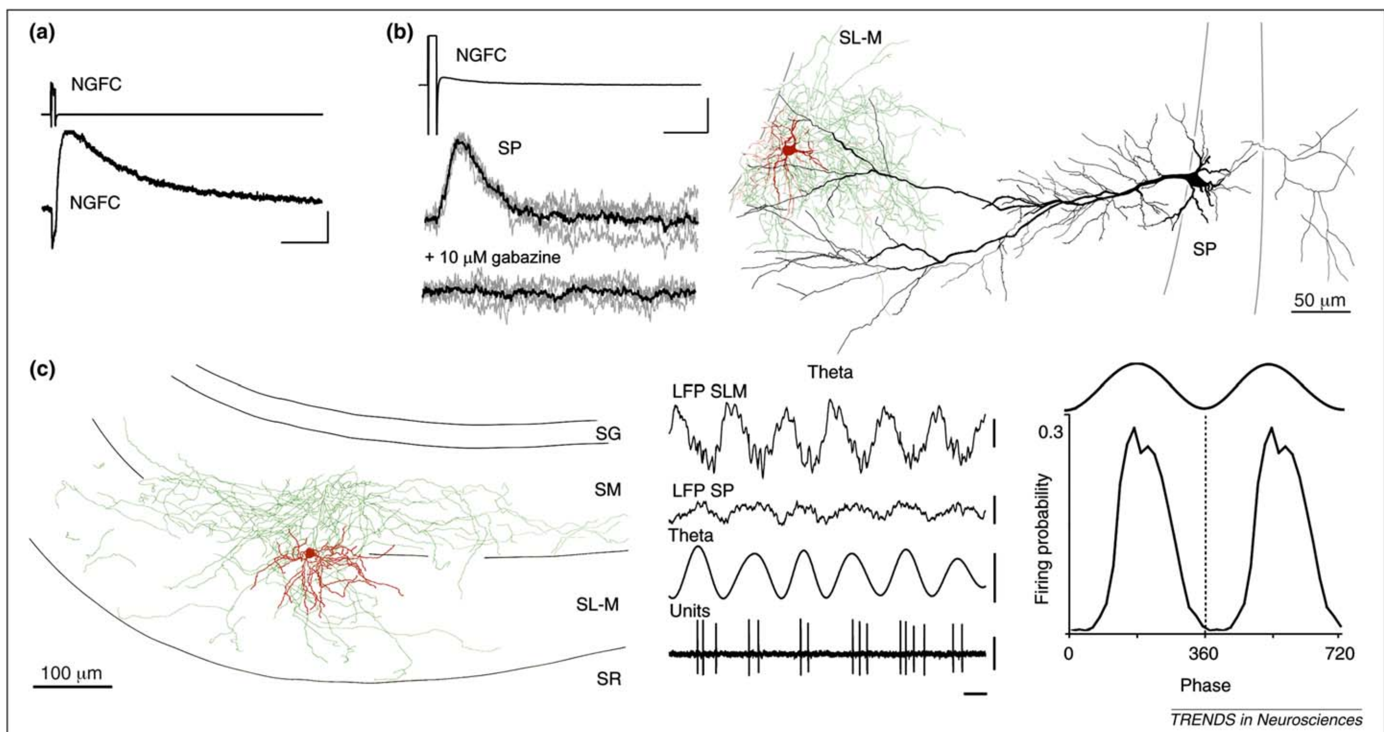

Figure 2. The neurogliaform cell (NGFC) is an interneuron type that mediates GABA$_{A,slow}$ in the hippocampus. **(a)** Inhibitory postsynaptic currents (IPSCs) recorded in voltage clamp in a NGFC (bottom trace) and evoked by an action current in another NGFC (upper trace) in an *in vitro* acute slice of rat hippocampus. The initial inward current flowing through the electrical synapse is followed by an outward current sensitive to a GABA$_A$ receptor antagonist (not shown). Calibration bars, 4 nA (upper trace), 20 pA (lower trace), 50 ms. **(b)** Whole-cell voltage-clamp recordings of IPSCs in a NGFC (upper trace) and a CA1 pyramidal cell (SP, middle trace) in a rat hippocampal acute slice in the presence of the GABA$_B$ receptor antagonist CGP55845. The GABA$_A$ receptor antagonist gabazine abolishes the IPSC in the CA1 pyramidal cell (bottom trace). Calibration bars, 0.5 nA (upper trace), 5 pA (lower trace), 50 ms. A partial reconstruction of the dendritic distribution of the recorded CA1 pyramidal cell is displayed on the right (black and grey lines) with the NGFC interneuron also depicted (red and green lines). **(c)** Axo-dendritic distribution and firing patterns of NGFCs recorded from rat hippocampus *in vivo*. Left, partial reconstruction of a NGFC; soma and dendrites complete (red), axonal arborization (green) from 5 coronal sections (60 μm each). Middle and right, firing patterns of the NGFC shown on the left during spontaneous network oscillations. Middle, example of traces of the local field potential (LFP, 0.3–300 Hz) or filtered LFP (theta, 3–6 Hz) and spike-train (units, 0.8–5 kHz) of a NGFC during theta waves. Note phase-reversal and amplitude differences between LFPs recorded from SP and SLM. Right, theta-phase firing-probability histograms for the NGFC; the same data are repeated in two cycles for theta histograms to indicate oscillations. Note that the maximal firing probability occurs at the peak of theta oscillations detected in the SP. Scale bars, LFP 1 mV, filtered theta 0.5 mV, units 0.5 mV, horizontal, theta 100 ms. SP, stratum pyramidale, SG, stratum granulosum, SM, stratum moleculare, SL-M, stratum lacunosum moleculare, SR, stratum radiatum. Panels (a–c) were adapted (with permission) from [31,32,44], respectively.

earlier studies that employed extracellular stimuli [4,22,23,43].

NGFCs and Ivy cells can be identified using an array of marker proteins, including α-actinin2, neuropeptide Y, neuronal nitric oxide synthase (nNOS), the transcription factor COUP-TFII, the extracellular matrix protein reelin, and GABA$_A$ receptor α_1 and δ subunits [28,31,33,44,45]. Subpopulations of heterogeneous embryologic origin exist – namely nNOS-positive NGFCs and all Ivy cells, which originate from the medial ganglionic eminence, and nNOS-negative NGFCs originating from the caudal ganglionic eminence [46]. The relevance of this taxonomy remains to be explored. NGFCs recorded *in vitro* from rat hippocampal slices display characteristic late firing when stimulated with a depolarizing current pulse just above threshold [31], whereas Ivy cells fire broad action potentials with frequency adaptation [33].

Currents with properties similar to hippocampal GABA$_{A,slow}$ have been detected in several brain areas. In the thalamus, slow sIPSCs are seen in GABAergic cells of the nucleus reticularis thalami (RTN). They are thought to originate from synaptic connections formed by their recurrent local collaterals [10]. In granule cells of the cerebellum, Golgi interneurons can evoke slow IPSCs [11] that gradually facilitate during high-frequency Golgi cell activity [12]. In the amygdala, slow unitary IPSCs have been observed in a few paired recordings of paracapsular intercalated cells [14], a group of GABAergic cells key in mediating fear-extinction in rodents [47]. This finding is consistent with the observation that extracellular stimulation of these neurons produces slow IPSCs in postsynaptic neurons of the central amygdala [13]. In the brainstem, slow GABA$_A$-receptor-mediated IPSCs have been recorded in the nucleus magnocellularis and are evoked by stimulation of the superior olivary nucleus axon terminals [15].

What accounts for the slow kinetics of GABA$_{A,slow}$?

The kinetics of a synaptic current are determined by the interaction between the spatiotemporal profile of the neurotransmitter and the intrinsic kinetic properties of the activated receptors. Each of these is in turn the product of numerous factors, such as the anatomical relationship between release sites and receptors, synchrony of vesicular release, transmitter diffusion and transport, transmembrane voltage, local ion concentrations, as well as receptor subunit composition, phosphorylation and other post-translational modifications. In addition, measurement error produced by imperfect voltage-clamp can influence apparent kinetic properties; this is particularly problematic for events that arise from distal dendritic sites.

Box 1. Does dendritic filtering account for $GABA_{A,slow}$?

Because $GABA_{A,slow}$ originates in the dendrites, but is usually recorded at the soma, could this slow current simply reflect inadequate space clamp (distortion due to dendritic filtering) [111,112], which can generate significant errors [113]? We first explain dendritic filtering and follow with experimental evidence arguing against this being the determinant of $GABA_{A,slow}$.

Dendritic filtering

- Somatic voltage-clamp imperfectly controls the membrane potential at the dendritic sites of pyramidal cells where $GABA_{A,slow}$ is generated [112,113].
- Because of the imperfect voltage-clamp, measured synaptic currents are attenuated, and are slower than the true conductance time-course, because capacitative charge that accumulates in the dendrites when channels are open then flows toward the soma even after the channels have closed.
- This attenuation can be counterbalanced by mechanisms that boost the currents along the dendrites, such as conductance-scaling and dendritic excitability [114,115].
- Computer simulations indicate that a current generated in the apical tuft of a CA1 pyramidal cell (~ 400 μm away from the soma), with t_{Rise} ~2 ms and t_{Decay} ~6 ms, increases to ~5 ms and ~13 ms, respectively, when recorded at the soma [112].

Evidence against dendritic filtering as the determinant of $GABA_{A,slow}$

- $GABA_{A,slow}$ conductance time-course has been measured using the voltage-jump method [4,116] (Figure I), which overcomes the distance-dependent distortion of synaptic currents. The method entails holding the cell at the chloride reversal potential during synaptic stimulation. In this case no current flows through open channels and no charge accumulates to later flow back to the soma as a distorted current. A delayed voltage-jump causes current to flow through those channels that remain open.
- Hippocampal NGFC-IPSCs are similarly slow in somatic recordings made from pyramidal cells [32], in recordings from more electrically compact postsynaptic interneurons with short dendrites [31], and in NGFC autapses [42].
- In the neocortex, Martinotti interneurons form synapses on cortical pyramidal cell dendrites at a greater distance from the soma than NGFCs, but they elicit faster IPSPs than NGFCs [30].
- In the hippocampus, the axons of O-LM cells and NGFCs make synapses onto the apical tuft of CA1 pyramidal cells [86], but the decay of the O-LM cell-evoked unitary IPSC in a CA1 pyramidal cell is faster than that evoked by NGFCs [117].

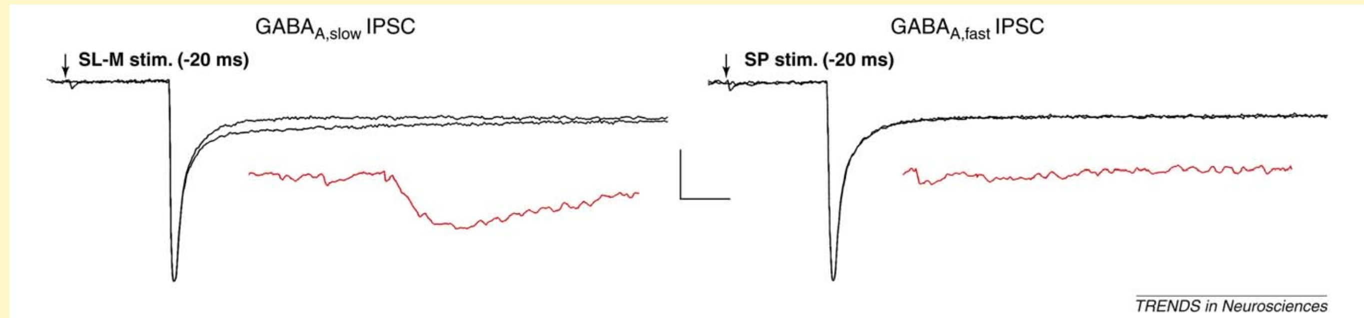

Figure I. Measuring the time-course of synaptic conductance. A pyramidal cell is held at the IPSC reversal potential of -60 mV in voltage clamp mode. Electrical stimuli are applied to stratum lacunosum-moleculare (SL-M) or stratum pyramidale (SP). Because there is no driving force at the chloride reversal potential, no current flows and no charge accumulates on the dendritic membrane to redistribute later to the cell body as a 'distorted IPSC'. After a brief delay the holding potential is stepped to −90 mV. Current flows through receptors that remain active (conducting) 20 ms after stimulating SL-M, as revealed by comparing the transient induced by the voltage jump following SL-M stimulation with the current induced by a voltage jump alone. The inset shows the subtracted traces (red). No conductance remains active 20 ms following SP stimulation. Calibration bars, 1 nA, 10 ms. Adapted with permission from [4].

However, the space clamp artifact does not appear to account for the slow kinetics of $GABA_{A,slow}$ (Box 1).

Given the large number of factors that can influence receptor kinetics, which of these are most influential in producing the characteristic slow rise and decay of $GABA_{A,slow}$? It appears that a number of different factors can come into play for different synapses, but that a combination of intrinsic properties produced by receptors of different subunit composition, together with a prolonged, spatially distributed, low-concentration spatiotemporal transmitter profile, endows most slow synapses with their defining kinetic characteristics.

$GABA_A$ receptor subunit composition

The subunit composition of $GABA_A$ receptors affects ligand affinity, channel gating and modulation, thereby shaping the kinetics of the resulting IPSCs [48]. The orthodox view is that phasic $GABA_{A,fast}$ IPSCs are mediated by low-affinity $GABA_A$ receptors, such as those composed of $\alpha_{1/2}\beta_{2/3}\gamma_2$ subunits clustered at synaptic sites, whereas tonic inhibition is mediated by high-affinity $GABA_A$ receptors containing α_4, α_5, α_6 and/or δ subunits located at extra- or peri-synaptic sites [48]. Because $GABA_{A,slow}$ displays intermediate features between phasic and tonic inhibition, it is possibly elicited by high-affinity receptors located at synaptic sites (Box 2; Glossary). This explanation could indeed hold in the thalamus, where there is a good correspondence between the expression of β_3 subunits in RTN neurons, which exhibit slow IPSCs, and β_2 subunits in relay cells of the ventrobasilar complex (VB), which express fast IPSCs. Fittingly, slow sIPSCs recorded from RTN neurons are virtually absent in β_3 subunit null mice at the same time that fast inhibition in VB cells is unchanged [8]. Direct measurements of slow GABA binding and unbinding rates thus support the conclusion that the long-lasting IPSCs of RTN neurons reflect the high affinity of the underlying receptors [9].

In the hippocampus of β_3 null mice, $GABA_{A,slow}$ recorded from CA1 pyramidal cells is also weak or absent [49]. A probable partner of β_3 subunits at these synapses is the α_5 subunit, and this preferentially associates with the β_3 subunit [50]. In addition to underlying tonic inhibition in these cells [51–54], α_5-subunit-containing receptors have been recently shown to contribute to spontaneous IPSCs [53–55] and to slow-evoked IPSCs produced by stimulation of the stratum lacunosum-moleculare (SLM)

Box 2. $GABA_A$ receptor subunit composition and synaptic localization

Subunit composition influences several $GABA_A$ receptor properties, including GABA sensitivity, kinetics, desensitization, subcellular location, and pharmacological profile. Classically, $GABA_{A,fast}$ signals are mediated by $GABA_A$ receptors comprised of low-affinity α-, β- and γ-subunits in the stoichiometry 2α:2β:1γ. By contrast, tonic inhibition is mediated by extrasynaptic high-affinity $GABA_A$ receptors expressing α_4, or α_6 subunits, with δ usually substituting for the γ subunit. Receptors composed of α_5 and γ subunits have also been demonstrated at extrasynaptic sites. The proposed differential expression of low- and high-affinity $GABA_A$ receptors at fast and slow synapses is depicted in Figure I.

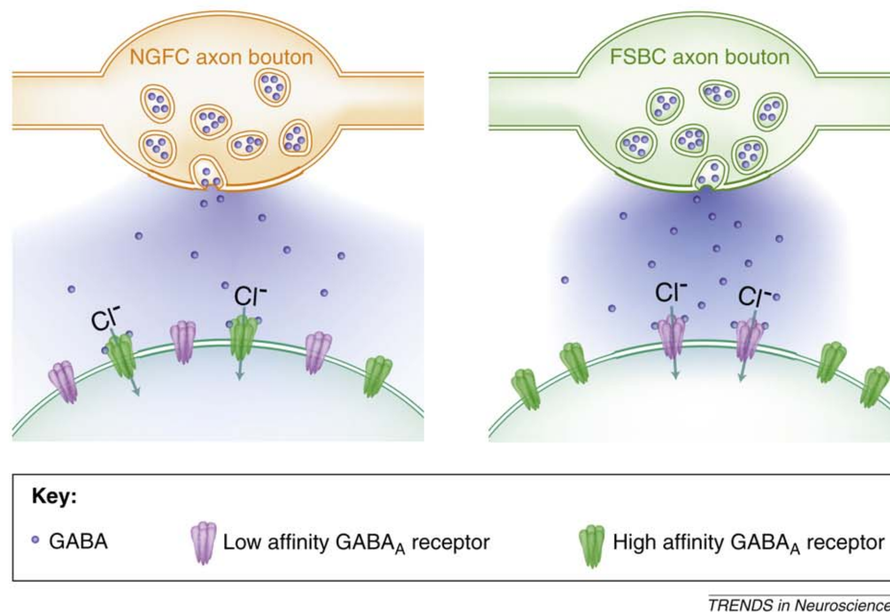

Figure I. Transmitter transients and $GABA_A$ receptors at fast and slow synapses. NGFC synapses mediating $GABA_{A,slow}$ can express both low- and high-affinity $GABA_A$ receptors, at both synaptic and extrasynaptic sites (left panel). Classical $GABA_{A,fast}$ synapses, such as those mediated by fast-spiking basket cells (FSBC), usually express low-affinity $GABA_A$ receptors at synapses and high-affinity receptors at extrasynaptic sites (right panel). The proposed broader spatial diffusion and lower concentration of GABA released from NGFC versus FSBC is also illustrated. Also note that the much larger cleft distance between the pre- to postsynaptic membranes that can be found at NGFC synapses compared to conventional inhibitory synapses (main text and Figure 3 for details) is not illustrated in this figure.

[53,55], NGFCs [42], or of the Schaffer collateral pathway [56]. Interestingly, dendrite-targeting interneurons of the neocortex also preferentially activate α_5-subunit-containing $GABA_A$ receptors, whereas those targeting the soma activate α_1-containing $GABA_A$ receptors [57]. Moreover, the δ subunit is found at slow synapses of dentate gyrus granule cells [43] and NGFCs [28].

Thus, several lines of evidence indicate that high-affinity receptors are present at $GABA_{A,slow}$ synapses. Does this mean that their intrinsically slow kinetics account for the long-lasting conductances at these synapses? Not necessarily. In β_3 null mice that lack slow IPSCs in pyramidal neurons, long-lasting inhibitory control of $GABA_{A,fast}$-generating hippocampal interneurons remains unaffected [49], indicating that receptors with a different subunit composition can also produce slow IPSCs. In pyramidal neurons these are likely to include non-α_5-containing receptors because some IPSCs recorded in mutant mice with benzodiazepine-insensitive α_5 subunits are still modulated by the benzodiazepine diazepam [55]. Furthermore, zolpidem and diazepam affect NGFC-IPSCs, suggesting that low-affinity $\alpha_{1/2}\beta_{2/3}\gamma_2$ $GABA_A$ receptors are present at NGFC synapses [42]. This functional result is consistent with recent immunohistochemical data showing that the α_1 subunit is highly enriched in hippocampal NGFC dendrites [44] that receive a substantial input from other NGFCs [31]. Taken together, the evidence indicates that intrinsic receptor kinetics could contribute to, but do not necessarily account for, the slow decay of hippocampal $GABA_{A,slow}$ IPSCs.

Spatiotemporal profile of extracellular GABA

If, unlike $GABA_{A,fast}$ currents [58], receptor identity itself does not dictate the kinetics of $GABA_{A,slow}$, what then accounts for the slow decay of this current? A clue could come from the finding that many drugs enhance the peak amplitude, but do not prolong the decay of slow IPSCs of NGFCs and pyramidal neurons [30,42,53,55]. At other synapses the propensity of drugs to increase slow IPSC amplitude has been attributed to receptor activation by a low peak concentration of neurotransmitter, as would be expected to occur with transmitter spillover to extrasynaptic sites. For example, at the Golgi cell to granule cell synapse in the cerebellum, slowly rising IPSCs are generated by extrasynaptic high-affinity α_6-containing $GABA_A$ receptors that sense a low concentration of GABA spilling out of remote synapses [11,12]. This might also be the case in the hippocampus [59].

GABA concentration at the synaptic cleft can influence the kinetics of unitary IPSCs [60], and the heterogeneous decay of mIPSCs at synapses that express a single subtype of $GABA_A$ receptor ($\alpha_1\beta_2\gamma_2$) [61] has been attributed to the

specific spatiotemporal profile of GABA concentration. Experimental evidence suggests that the extended presence of a low concentration of extracellular GABA, perhaps influenced by an unusually large synaptic cleft, contributes to the slow kinetics of $GABA_{A,slow}$ at NGFC synapses [28,30,42] (Figure 3). A single NGFC axon has a release site density comparable to that of five or six basket-cell axons [28], and it therefore produces a cloud of activation in which GABA released from NGFC axons reaches synaptic and non-synaptic receptors. Axon boutons of NGFCs are often [28], but not always [7,31,44], found 1–5 μm away from target dendrites, a surprisingly long distance compared to the 10–20 nm of conventional synapses. GABA released from NGFCs also can inhibit the release of glutamate or GABA from axon terminals located remotely from NGFC release sites [28].

Thus, the picture that emerges from these studies is one of volume transmission [62] wherein a widespread, prolonged, low-level GABA transient is produced by a dense array of NGFC release sites. This leads to a slowly decaying conductance increase in nearby dendrites of pyramidal neurons, NGFCs, and other interneurons. A number of additional observations are consistent with this scenario, including (i) a single NGFC action potential elicits not only a $GABA_A$ receptor-mediated synaptic response but also a response mediated by peri-synaptic $GABA_B$ receptors

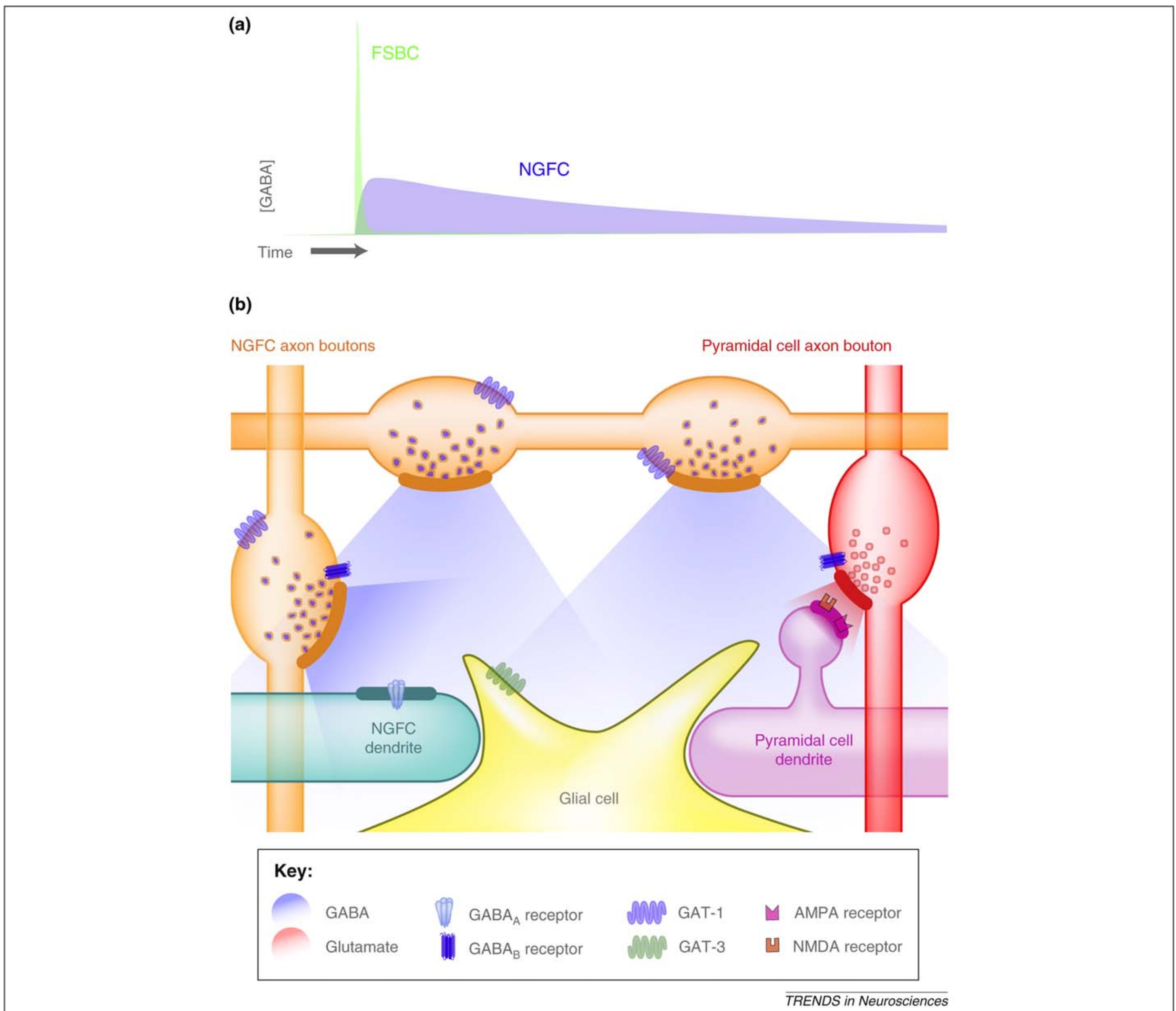

Figure 3. Volume transmission produces neurogliaform cell (NGFC)-mediated $GABA_{A,slow}$ IPSCs. **(a)** A GABA transient of lower concentration but greater duration is present at NGFC synapses compared with fast-spiking basket cell (FSBC) synapses in the hippocampus [42]. **(b)** Schematic diagram illustrating the main ultrastructural features proposed to underlie volume transmission by NGFCs. NGFCs do not seem to require direct synaptic junctions to affect target cells [28]. A non-synaptic apposition is shown for two NGFC axon boutons (top, orange) and the dendritic shaft of a postsynaptic NGFC (bottom left, green). Heterosynaptic modulation also takes place via $GABA_B$ receptors expressed at both glutamatergic (middle right, red) and GABAergic (middle left, orange) axon endings. In addition, NGFC axon boutons display conventional synapses (middle left, orange bouton and lower left, green dendrite) as revealed by electron microscopy [7,31,44]. A glial cell is also illustrated because of its probable involvement in NGFC-mediated signaling; the details of this interaction are not yet known. GABA transporters (GAT-1 and GAT-3) are responsible for the uptake of extracellular GABA and are expressed in NGFCs and glial cells. AMPA and NMDA glutamate receptors are depicted only in pyramidal cells.

[7,31,32], (ii) GABA uptake blockers not only enhance $GABA_{A,slow}$ in pyramidal neurons [23] but also augment responses mediated by $GABA_B$ receptors expressed at extrasynaptic sites [30], and (iii) low-affinity $GABA_A$ receptor antagonists have a greater effect on $GABA_{A,slow}$ versus $GABA_{A,fast}$ [30,42]. In simulations, NGFC-IPSCs are best replicated using a low-concentration (8–20 μM) but persistent (t_{Decay} 35–73 ms) GABA transient [42]. It is possible that the functional impact of the diffuse 'GABA cloud' produced by a single NGFC is further amplified by electrical coupling with other NGFCs [31] and with other types of interneurons [63].

Interestingly, synaptic vesicles far from synaptic specializations have been observed in the axonal plexus of both NGFCs and Ivy cells [28,33], supporting the likelihood of extrasynaptic transmitter release. This structural arrangement might be related to the threefold longer duration of Ca^{2+} transients in axonal boutons of NGFCs compared to other types of hippocampal interneurons [42].

Other potential mechanisms underlying $GABA_{A,slow}$

In addition to receptor-mediated conductances, other voltage-dependent neuronal properties can shape synaptic potentials. In neocortex, for example, IPSPs are augmented at depolarized membrane voltages when IPSPs deactivate tonically-active sodium channels [64]. In the hippocampus the hyperpolarization-activated cation current, I_h, reduces slow IPSP amplitude at hyperpolarized potentials and accelerates its decay, and the persistent sodium current, I_{NAP}, increases the amplitude of slow IPSPs at depolarized subthreshold potentials [65]. Because $GABA_A$ receptors are only weakly voltage-dependent, these effects are not expected to have a substantial impact on the conductance profile of slow synapses under voltage clamp, but they could certainly influence their impact on integrative cellular function.

The time-course of postsynaptic currents at several CNS synapses changes during development. For example, the time-course of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor excitatory postsynaptic currents (EPSCs) becomes significantly faster during maturation [66] due to changes in synaptic structure in cerebellar granule cells [67]. The decay of fast mIPSCs in hippocampal CA1 pyramidal cells accelerates during development [25]. Surprisingly, the kinetics of slow mIPSCs are unchanged during this same period [25]. Therefore their slow duration cannot be attributed to a developmental process at inhibitory synapses onto CA1 pyramidal cells. Remarkably, slow IPSCs are the first synaptic signals detected in recordings from immature hippocampal granule cells [68]. Slow IPSCs in newborn hippocampal granule cells have kinetics similar to those of mature granule cells [69], most likely arising from NGFCs [31].

Long lasting IPSCs can also be generated by asynchronous release of transmitter occurring at significant delays after a presynaptic action potential, as reported at certain inhibitory GABAergic and glycinergic synapses [70–72]. This phenomenon is particularly pronounced when cholecystokinin (CCK)-expressing interneurons in the rat dentate gyrus [71] or inhibitory synapses of the avian and rat dorsal cochlear nucleus [70,72] are stimulated with behaviorally-relevant high-frequency patterns.

Role of $GABA_{A,slow}$ in neuronal networks

Given the striking differences between the kinetics of $GABA_{A,fast}$ and $GABA_{A,slow}$, these two different forms of phasic inhibition would be expected to play distinct functional roles. In the thalamus, slow inhibitory connections within the RTN are thought to be instrumental in generating network oscillations. When slow IPSCs are compromised, as in mice lacking the $GABA_A$ receptor β_3 subunit, activity changes from a partially synchronous spindle-like pattern to hypersynchronous epileptic discharges [8]. This finding, supported by a modeling study in which the slow decay of currents at RTN neurons was found to be pivotal for its ability to prevent epileptiform activity [73], suggests that intra-RTN inhibition plays a role in restricting activity during sensory processing or in states of focused arousal [74].

A number of characteristics make $GABA_{A,slow}$ IPSCs well-suited to play a role in the modulation of synaptic plasticity [5,75]. In CA1 pyramidal neurons, the location of their synapses is associated with the major afferent excitatory inputs – thalamic and entorhinal cortex afferents on the apical dendritic tuft in the SLM [76] (NGFCs) and the Schaffer collateral pathway from CA3 on diagonal branches of mid-apical dendrites in the stratum radiatum (Ivy cells). Here, their slow time-course matches that of N-methyl-D-aspartate (NMDA)-receptor EPSPs, so they are able to maintain dendritic hyperpolarization. They can also suppress calcium-dependent spikes [77] and sodium spike back-propagation from the soma to the dendrites [78].

The use-dependence of $GABA_{A,slow}$ could also contribute to its ability to control synaptic plasticity. Stimuli presented in short succession result in a prominent $GABA_B$ receptor-mediated short-term depression of slow IPSPs [79]. Accordingly, $GABA_B$ antagonists partially rescue short-term depression after stimulation of NGFCs with short trains of stimuli [28,31,32]. The dendritic disinhibition produced by presynaptic $GABA_B$ receptors is maximal when stimuli are repeated at theta frequency [31]. This unopposed excitation contributes to the ability of appropriately patterned stimuli to produce synaptic plasticity [80]. When NGFC action potentials occurring during theta oscillations *in vivo* are re-enacted in NGFC *in vitro*, they elicit a fast and robust (time constant ~10 s), but reversible (time constant recovery ~10 min), mid-term synaptic depression of the IPSCs, mostly attributable to receptor desensitization [42]. The depression is not complete, but ~80% at steady-state [42]. Such a mechanism could provide a means for controlling the inhibitory circuitry that modulates synaptic plasticity, although further studies are required to demonstrate this.

The influence of $GABA_{A,slow}$ in the hippocampal CA1 region extends to the generation and control of network oscillations. Theta (4–8 Hz) oscillations, which are prominent in the hippocampus, are observed during rapid eye movement (REM) sleep, arousal, locomotion, and other voluntary behaviors [81]. They are thought to play crucial functions in memory formation and recall [81]. Gamma

(25–70 Hz) oscillations, which are present in the hippocampus [82] and cortex [83], are associated with sensory processing and are thought to integrate perceptual features. These network oscillations could regulate the strength of neuronal signals and assist in encoding and/or retrieving information in neuronal networks [84].

In the same way that the rapid decay of the $GABA_{A,fast}$ (t_{Decay} ~10 ms) is thought be instrumental in setting the rhythm of the faster gamma oscillations [26], the extended decay of $GABA_{A,slow}$ (t_{Decay} ~60 ms) might contribute to the slower theta oscillations. Interestingly, theta oscillations are most regular in frequency, and have the largest amplitude, in the SLM of CA1 [82,85], where NGFCs are located. *In vivo,* the firing of NGFCs is time-locked to the peak of the theta cycle, coincident with the synaptic volley from the entorhinal cortex [44]. In addition, NGFCs and other interneurons of the SLM are monosynaptically inhibited by interneurons of the stratum oriens, such as the oriens-lacunosum-moleculare (O-LM) cell [86]. Coupled with an intrinsic theta-frequency resonance of pyramidal neurons and interneurons of the SLM [87], including NGFCs [44], these inhibitory synapses are thus likely to contribute to the generation of theta oscillations [82,88].

A classical model of hippocampal theta rhythm includes two phasic dipoles: an extrinsic input from the entorhinal cortex, and another from the medial septum via local interneurons targeting the soma of pyramidal cells [89] (but see [81]). There is evidence that $GABA_{A,slow}$ bridges these two dipoles [90] (Figure 4). Projections from the entorhinal cortex terminate in the SLM [91] and excite the distal dendrites of CA1 pyramidal cells [92] as well as interneurons (including NGFCs), mediating robust feed-forward

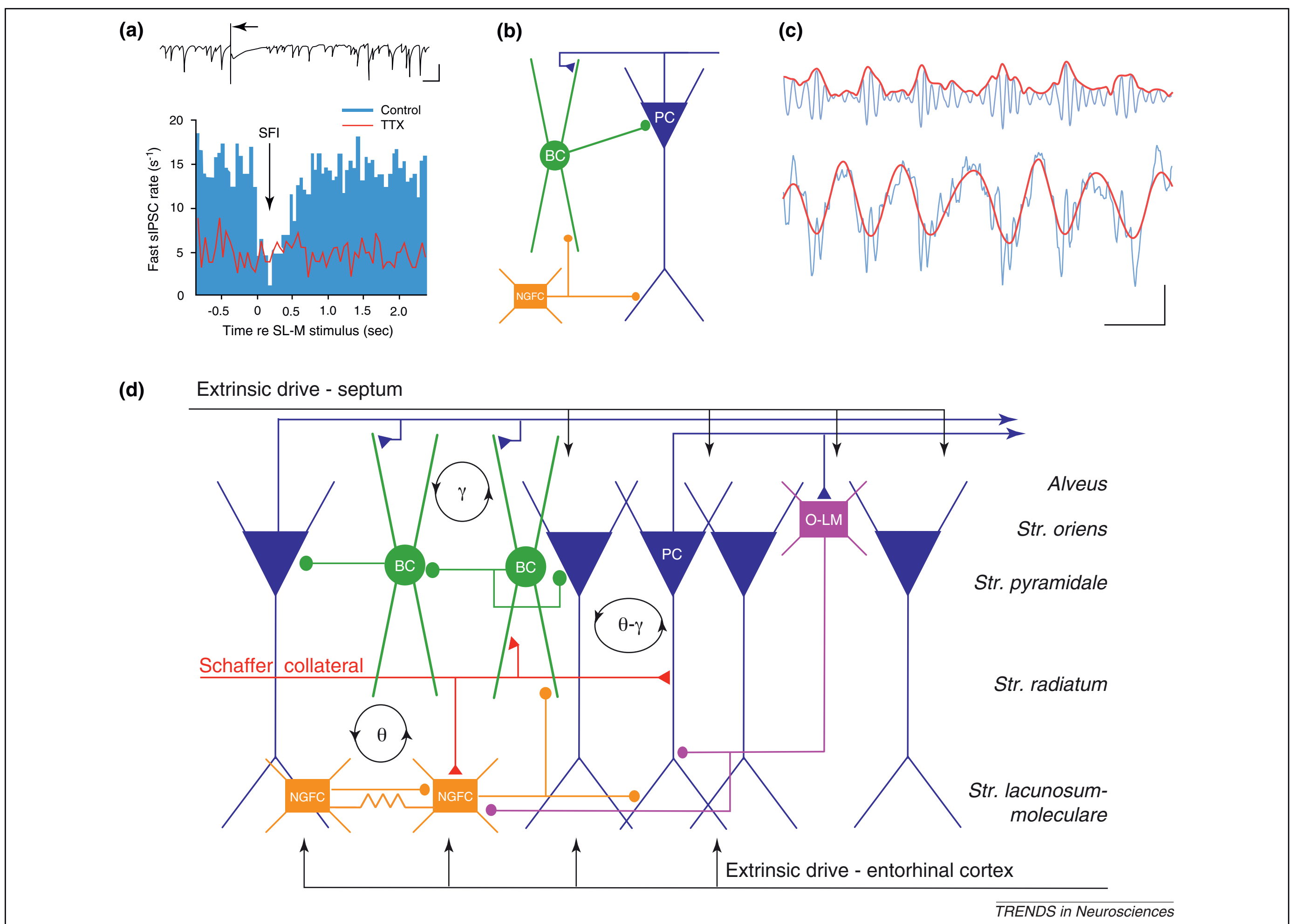

Figure 4. Role of $GABA_{A,slow}$ in CA1 hippocampal circuitry. **(a)** Stimulation of SL-M (note the stimulus artefact indicated by an arrow in the upper trace) evokes a $GABA_{A,slow}$ IPSC immediately after the stimulation followed by a reduction in the rate and amplitude of fast sIPSCs; it thus induces suppression of fast inhibition (SFI) in a CA1 pyramidal cell. Calibration bars, 100 ms, 50 pA. Frequency histograms of sIPSCs under control conditions (blue) and mIPSCs in the presence of 1 μM TTX (red). Note that during SFI the sIPSC rate is decreased to the rate recorded in TTX. Modified, with permission, from [90]. **(b)** Minimal neuronal network underlying SFI. Stimulation of neurogliaform cells (NGFC) inhibits pyramidal cells (PC) and basket cells (BC), the latter generating fast IPSCs leading to SFI in the PC. **(c)** Gamma oscillation nested into theta oscillations. Top, gamma-filtered oscillations (blue trace) and gamma envelope (red trace); bottom: wide-bandpass signal (blue trace) and theta-filtered oscillations (red trace). Note the modulation of gamma-oscillation amplitude at theta frequency. Calibration bars, 0.5 mV, 100 ms. Adapted with permission from [49]. **(d)** Simplified scheme of neuronal circuitry within CA1 rat hippocampus. For a more complete scheme see [26]. Two distinct current generators (dipoles) can generate theta rhythm in the hippocampus. An excitatory generator formed by rhythmic excitation from the entorhinal cortex produces an active sink in the distal dendritic domain of PCs. An inhibitory perisomatic dipole is generated by local interneurons that are phasically inhibited by GABAergic cells of the medial septum. For further details and limitations of this model see [81]. Hippocampal NGFCs that mediate $GABA_{A,slow}$ (and are also coupled via electrical synapses) are well placed to create a link between these two dipoles and to modulate the amplitude of gamma activity produced by BCs [31,32,63,90,97]. Only selected cell types are shown in the simplified scheme. O-LM, oriens-lacunosum moleculare cell.

inhibition [32,93,94]. These interneurons of SLM rhythmically inhibit somatically projecting interneurons at theta frequency, resulting in the suppression of fast inhibition (SFI) of CA1 pyramidal cells [90]. In this way, interneurons of the SLM can generate dendritic inhibition and SFI of CA1 pyramidal cells at the same time. This model is consistent with the observation that dendritic theta is 180° out of phase with somatic theta [95] because pyramidal cell dendrites are inhibited when the rhythmic theta frequency inhibition of pyramidal cell somata is relieved by SFI. During active exploratory behavior in rodents, gamma oscillations wax and wane at theta frequency, a phenomenon called nested theta–gamma activity [96]. This model correctly predicts that pyramidal cells will fire maximally after both $GABA_{A,slow}$ inhibition of pyramidal cell dendrites and SFI have decayed back to baseline, and thus during the nested theta–gamma inhibition provided by $GABA_{A,fast}$ interneurons [96]. Computer simulations confirm that networks of interneurons generating fast and slow IPSPs can shape mixed gamma–theta rhythms [97]. Observed alterations in theta, gamma and nested theta–gamma oscillations in β_3 null mice that display impaired $GABA_{A,slow}$ responses further support this theoretical framework [49].

Whereas NGFCs fire preferentially at the peak of each theta oscillation [44], Ivy cells fire preferentially at the trough of each oscillation recorded in the stratum pyramidale [33]. This timing could be instrumental in separating the influence of enthorinal cortex input versus CA3 input onto CA1 pyramidal neurons during different phases of the theta oscillation, as required for accurate memory encoding and retrieval, according to a computational model of hippocampal learning [98].

$GABA_{A,slow}$ and therapeutic potential for general anesthetics and cognitive-enhancing drugs

The $GABA_A$ receptor is a molecular target for many clinically-used drugs, including general anesthetics [99]. A signature effect of many anesthetics is the prolongation of the decay phase of $GABA_{A,fast}$ IPSCs [24,100–102]. Similar effects are seen at $GABA_{A,slow}$ synapses [24,103,104]. Interestingly, the frequency of slow sIPSCs recorded from hippocampal CA1 pyramidal cells *in vitro* has been shown to be selectively enhanced by the abused inhalant toluene [105].

The general anesthetic etomidate has been demonstrated to preferentially enhance $GABA_{A,slow}$ inhibition at concentrations associated with amnesia *in vivo* [104]. This result is particularly intriguing given the finding that learning and memory is enhanced in mice that either lack the $GABA_A$ receptor α_5 subunit [106] or that carry a point mutation reducing its expression in the hippocampus [107]. Although the α_5 subunit is expressed in the hippocampus at extrasynaptic sites mediating tonic inhibition [51], it is also found at dendritic $GABA_{A,slow}$ synapses [42,53,55–57]. $GABA_A$ receptors containing the α_5 subunit are being intensively studied as novel targets for memory-blocking and cognition-enhancing drugs [108,109]. This could have important clinical implications, such as in Alzheimer's disease (AD), where hippocampal α_5-containing $GABA_A$ receptors have been demonstrated to be relatively spared in the hippocampus of AD patients [110].

Box 3. Outstanding questions

- Subunit composition, trafficking, lateral movements, and functional characteristics of $GABA_A$ receptors are dynamically regulated by intracellular proteins, post-translational modifications and diverse signaling pathways [118]. How do these factors affect $GABA_{A,slow}$?
- Would it be possible to detect $GABA_{A,slow}$ directly at small distal dendritic branches by using optical methods, such as voltage-sensitive dye imaging [119]?
- A long-lasting and diffuse extracellular GABA transient underlies NGFC-IPSCs [30,42]. How is this spatiotemporal profile formed? What are its principal characteristics?
- NGFCs form both conventional synapses [7,31,44] and *en passant* boutons found up to 5 μm from target dendrites [28]. Do these two different types of synapses both produce IPSCs with slow kinetics, or do they have different functions?
- NGFC processes are found near blood vessels [32,120], and activation of NGFCs or other interneuron types within the cortex can change the luminal diameter of neighboring microvessels [120]. What are the mechanisms underlying neurovascular coupling? Does this involve signaling between NGFC and glial cells?
- NGFCs and Ivy cells fire repeatedly during theta oscillations *in vivo* [33,44], but the same activity re-enacted in a NGFC *in vitro* evokes slow IPSCs that are strongly reduced in their amplitude after only a few stimuli and then recover after several minutes [42]. Do slow IPSCs remain effective during periods of high firing-rates *in vivo*?
- $GABA_{A,slow}$ synapses are well-suited to control synaptic plasticity. Under what physiological or pharmacological conditions do these synapses influence learning and memory, and can they be manipulated for therapeutic benefit?

Therefore, $GABA_{A,slow}$ could represent a novel target for cognition-enhancing drugs.

Conclusions

Since the initial report of $GABA_{A,slow}$ IPSCs in the hippocampus, slow $GABA_A$ receptor-mediated IPSCs have been found throughout the CNS and substantial progress has been made in understanding the underlying causes and subsequent consequences of this particular form of synaptic inhibition. The discovery that NGFCs and Ivy cells mediate $GABA_{A,slow}$ sets these interneurons apart from classical 'fast-acting' interneurons, such as fast-spiking basket cells. A number of functional roles for $GABA_{A,slow}$ have been suggested, such as being involving in modulating synaptic plasticity and the generation of slow network oscillations. Additional targets that could be affected by such inhibition include glial cells and blood vessels, via neurovascular coupling with NGFCs. Continuing research on $GABA_{A,slow}$ will advance our knowledge of inhibitory synaptic transmission and neuronal circuitry (Box 3). Such research should also provide novel molecular targets for the future development of therapeutics to modulate synaptic transmission and plasticity.

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References

1 Coombs, J.S. *et al.* (1955) The specific ionic conductances and the ionic movements across the motoneuronal membrane that produce the inhibitory post-synaptic potential. *J. Physiol.* 130, 326–374

2 Farrant, M. and Nusser, Z. (2005) Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat. Rev. Neurosci.* 6, 215–229
3 Kaneda, M. *et al.* (1995) Whole-cell and single-channel currents activated by GABA and glycine in granule cells of the rat cerebellum. *J. Physiol.* 485, 419–435
4 Pearce, R.A. (1993) Physiological evidence for two distinct GABAA responses in rat hippocampus. *Neuron* 10, 189–200
5 Kapur, A. *et al.* (1997) GABAA-mediated IPSCs in piriform cortex have fast and slow components with different properties and locations on pyramidal cells. *J. Neurophysiol.* 78, 2531–2545
6 Sceniak, M.P. and Maciver, M.B. (2008) Slow GABA(A) mediated synaptic transmission in rat visual cortex. *BMC Neurosci.* 9, 8
7 Tamas, G. *et al.* (2003) Identified sources and targets of slow inhibition in the neocortex. *Science* 299, 1902–1905
8 Huntsman, M.M. *et al.* (1999) Reciprocal inhibitory connections and network synchrony in the mammalian thalamus. *Science* 283, 541–543
9 Schofield, C.M. and Huguenard, J.R. (2007) GABA affinity shapes IPSCs in thalamic nuclei. *J. Neurosci.* 27, 7954–7962
10 Zhang, S.J. *et al.* (1997) GABAA receptor-mediated Cl^- currents in rat thalamic reticular and relay neurons. *J. Neurophysiol.* 78, 2280–2286
11 Rossi, D.J. and Hamann, M. (1998) Spillover-mediated transmission at inhibitory synapses promoted by high affinity alpha6 subunit GABA(A) receptors and glomerular geometry. *Neuron* 20, 783–795
12 Crowley, J.J. *et al.* (2009) Dynamics of fast and slow inhibition from cerebellar Golgi cells allow flexible control of synaptic integration. *Neuron* 63, 843–853
13 Delaney, A.J. and Sah, P. (2001) Pathway-specific targeting of GABA(A) receptor subtypes to somatic and dendritic synapses in the central amygdala. *J. Neurophysiol.* 86, 717–723
14 Geracitano, R. *et al.* (2007) Synaptic heterogeneity between mouse paracapsular intercalated neurons of the amygdala. *J. Physiol.* 585, 117–134
15 Kuo, S.P. *et al.* (2009) Heterogeneous kinetics and pharmacology of synaptic inhibition in the chick auditory brainstem. *J. Neurosci.* 29, 9625–9634
16 Bacci, A. *et al.* (2003) Major differences in inhibitory synaptic transmission onto two neocortical interneuron subclasses. *J. Neurosci.* 23, 9664–9674
17 Hajos, N. and Mody, I. (1997) Synaptic communication among hippocampal interneurons: properties of spontaneous IPSCs in morphologically identified cells. *J. Neurosci.* 17, 8427–8442
18 Houston, C.M. *et al.* (2009) Intracellular chloride ions regulate the time course of GABA-mediated inhibitory synaptic transmission. *J. Neurosci.* 29, 10416–10423
19 Otis, T.S. and Mody, I. (1992) Modulation of decay kinetics and frequency of GABAA receptor-mediated spontaneous inhibitory postsynaptic currents in hippocampal neurons. *Neuroscience* 49, 13–32
20 Edwards, F.A. *et al.* (1990) Quantal analysis of inhibitory synaptic transmission in the dentate gyrus of rat hippocampal slices: a patch-clamp study. *J. Physiol.* 430, 213–249
21 Nusser, Z. *et al.* (1999) Differential regulation of synaptic GABAA receptors by cAMP-dependent protein kinase in mouse cerebellar and olfactory bulb neurones. *J. Physiol.* 521, 421–435
22 Ouardouz, M. and Lacaille, J.C. (1997) Properties of unitary IPSCs in hippocampal pyramidal cells originating from different types of interneurons in young rats. *J. Neurophysiol.* 77, 1939–1949
23 Banks, M.I. *et al.* (1998) The synaptic basis of GABAA,slow. *J. Neurosci.* 18, 1305–1317
24 Pearce, R.A. (1996) Volatile anaesthetic enhancement of paired-pulse depression investigated in the rat hippocampus *in vitro*. *J. Physiol.* 492, 823–840
25 Banks, M.I. *et al.* (2002) Development of GABA(A) receptor-mediated inhibitory postsynaptic currents in hippocampus. *J. Neurophysiol.* 88, 3097–3107
26 Klausberger, T. and Somogyi, P. (2008) Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* 321, 53–57
27 Megias, M. *et al.* (2001) Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells. *Neuroscience* 102, 527–540
28 Olah, S. *et al.* (2009) Regulation of cortical microcircuits by unitary GABA-mediated volume transmission. *Nature* 461, 1278–1281
29 Olah, S. *et al.* (2007) Output of neurogliaform cells to various neuron types in the human and rat cerebral cortex. *Front. Neural Circuits* 1, 4
30 Szabadics, J. *et al.* (2007) Different transmitter transients underlie presynaptic cell type specificity of GABAA,slow and GABAA,fast. *Proc. Natl. Acad. Sci. U. S. A.* 104, 14831–14836
31 Price, C.J. *et al.* (2005) Neurogliaform neurons form a novel inhibitory network in the hippocampal CA1 area. *J. Neurosci.* 25, 6775–6786
32 Price, C.J. *et al.* (2008) GABA(B) receptor modulation of feedforward inhibition through hippocampal neurogliaform cells. *J. Neurosci.* 28, 6974–6982
33 Fuentealba, P. *et al.* (2008) Ivy cells: a population of nitric-oxide-producing, slow-spiking GABAergic neurons and their involvement in hippocampal network activity. *Neuron* 57, 917–929
34 Ramon y Cajal, S. (1893) Estructura del asta de Ammon y fascia dentata. *Anal. Soc. Espan. Hist. Nat.* 22, 53–114
35 Valverde, F. (1971) Short axon neuronal subsystems in the visual cortex of the monkey. *Int. J. Neurosci.* 1, 181–197
36 Jones, E.G. (1975) Varieties and distribution of non-pyramidal cells in the somatic sensory cortex of the squirrel monkey. *J. Comp. Neurol.* 160, 205–267
37 Kisvarday, Z.F. *et al.* (1990) Synapses, axonal and dendritic patterns of GABA-immunoreactive neurons in human cerebral cortex. *Brain* 113, 793–812
38 Hestrin, S. and Armstrong, W.E. (1996) Morphology and physiology of cortical neurons in layer I. *J. Neurosci.* 16, 5290–5300
39 Kawaguchi, Y. and Kubota, Y. (1997) GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb. Cortex* 7, 476–486
40 Vida, I. *et al.* (1998) Unitary IPSPs evoked by interneurons at the stratum radiatum–stratum lacunosum-moleculare border in the CA1 area of the rat hippocampus *in vitro*. *J. Physiol.* 506, 755–773
41 Khazipov, R. *et al.* (1995) Hippocampal CA1 lacunosum-moleculare interneurons: modulation of monosynaptic GABAergic IPSCs by presynaptic GABAB receptors. *J. Neurophysiol.* 74, 2126–2137
42 Karayannis, T. *et al.* (2010) Slow GABA transient and receptor desensitization shape synaptic responses evoked by hippocampal neurogliaform cells. *J. Neurosci.* 30, 9898–9909
43 Wei, W. *et al.* (2003) Perisynaptic localization of delta subunit-containing GABA(A) receptors and their activation by GABA spillover in the mouse dentate gyrus. *J. Neurosci.* 23, 10650–10661
44 Fuentealba, P. *et al.* (2010) Expression of COUP-TFII nuclear receptor in restricted GABAergic neuronal populations in the adult rat hippocampus. *J. Neurosci.* 30, 1595–1609
45 Szabadics, J. and Soltesz, I. (2009) Functional specificity of mossy fiber innervation of GABAergic cells in the hippocampus. *J. Neurosci.* 29, 4239–4251
46 Tricoire, L. *et al.* (2010) Common origins of hippocampal Ivy and nitric oxide synthase expressing neurogliaform cells. *J. Neurosci.* 30, 2165–2176
47 Amano, T. *et al.* (2010) Synaptic correlates of fear extinction in the amygdala. *Nat. Neurosci.* 13, 489–494
48 Farrant, M. and Kaila, K. (2007) The cellular, molecular and ionic basis of GABA(A) receptor signalling. *Prog. Brain Res.* 160, 59–87
49 Hentschke, H. *et al.* (2009) Altered GABAA,slow inhibition and network oscillations in mice lacking the GABAA receptor beta3 subunit. *J. Neurophysiol.* 102, 3643–3655
50 Ju, Y.H. *et al.* (2009) Distinct properties of murine alpha 5 gamma-aminobutyric acid type a receptors revealed by biochemical fractionation and mass spectroscopy. *J. Neurosci. Res* 87, 1737–1747
51 Caraiscos, V.B. *et al.* (2004) Tonic inhibition in mouse hippocampal CA1 pyramidal neurons is mediated by alpha5 subunit-containing gamma-aminobutyric acid type A receptors. *Proc. Natl. Acad. Sci. U. S. A.* 101, 3662–3667
52 Scimemi, A. *et al.* (2005) Multiple and plastic receptors mediate tonic GABAA receptor currents in the hippocampus. *J. Neurosci.* 25, 10016–10024
53 Prenosil, G.A. *et al.* (2006) Specific subtypes of GABAA receptors mediate phasic and tonic forms of inhibition in hippocampal pyramidal neurons. *J. Neurophysiol.* 96, 846–857
54 Glykys, J. and Mody, I. (2006) Hippocampal network hyperactivity after selective reduction of tonic inhibition in GABA A receptor alpha5 subunit-deficient mice. *J. Neurophysiol.* 95, 2796–2807

55 Zarnowska, E.D. *et al.* (2009) GABAA receptor alpha5 subunits contribute to GABAA,slow synaptic inhibition in mouse hippocampus. *J. Neurophysiol.* 101, 1179–1191
56 Vargas-Caballero, M. *et al.* (2010) alpha5 Subunit-containing GABA(A) receptors mediate a slowly decaying inhibitory synaptic current in CA1 pyramidal neurons following Schaffer collateral activation. *Neuropharmacology* 58, 668–675
57 Ali, A.B. and Thomson, A.M. (2008) Synaptic alpha 5 subunit-containing GABAA receptors mediate IPSPs elicited by dendrite-preferring cells in rat neocortex. *Cereb. Cortex* 18, 1260–1271
58 Vicini, S. *et al.* (2001) GABA(A) receptor alpha1 subunit deletion prevents developmental changes of inhibitory synaptic currents in cerebellar neurons. *J. Neurosci.* 21, 3009–3016
59 Isaacson, J.S. *et al.* (1993) Local and diffuse synaptic actions of GABA in the hippocampus. *Neuron* 10, 165–175
60 Barberis, A. *et al.* (2004) Presynaptic source of quantal size variability at GABAergic synapses in rat hippocampal neurons in culture. *Eur. J. Neurosci.* 20, 1803–1810
61 Nusser, Z. *et al.* (2001) Synapse-specific contribution of the variation of transmitter concentration to the decay of inhibitory postsynaptic currents. *Biophys. J.* 80, 1251–1261
62 Vizi, E.S. *et al.* (2010) Non-synaptic receptors and transporters involved in brain functions and targets of drug treatment. *Br. J. Pharmacol.* 160, 785–809
63 Zsiros, V. and Maccaferri, G. (2005) Electrical coupling between interneurons with different excitable properties in the stratum lacunosum-moleculare of the juvenile CA1 rat hippocampus. *J. Neurosci.* 25, 8686–8695
64 Stuart, G. (1999) Voltage-activated sodium channels amplify inhibition in neocortical pyramidal neurons. *Nat. Neurosci.* 2, 144–150
65 Hardie, J.B. and Pearce, R.A. (2006) Active and passive membrane properties and intrinsic kinetics shape synaptic inhibition in hippocampal CA1 pyramidal neurons. *J. Neurosci.* 26, 8559–8569
66 Bellingham, M.C. *et al.* (1998) Developmental changes in EPSC quantal size and quantal content at a central glutamatergic synapse in rat. *J. Physiol.* 511, 861–869
67 Cathala, L. *et al.* (2005) Changes in synaptic structure underlie the developmental speeding of AMPA receptor-mediated EPSCs. *Nat. Neurosci.* 8, 1310–1318
68 Esposito, M.S. *et al.* (2005) Neuronal differentiation in the adult hippocampus recapitulates embryonic development. *J. Neurosci.* 25, 10074–10086
69 Markwardt, S.J. *et al.* (2009) Input-specific GABAergic signaling to newborn neurons in adult dentate gyrus. *J. Neurosci.* 29, 15063–15072
70 Balakrishnan, V. *et al.* (2009) Slow glycinergic transmission mediated by transmitter pooling. *Nat. Neurosci.* 12, 286–294
71 Hefft, S. and Jonas, P. (2005) Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron-principal neuron synapse. *Nat. Neurosci.* 8, 1319–1328
72 Lu, T. and Trussell, L.O. (2000) Inhibitory transmission mediated by asynchronous transmitter release. *Neuron* 26, 683–694
73 Sohal, V.S. *et al.* (2000) Reciprocal inhibitory connections regulate the spatiotemporal properties of intrathalamic oscillations. *J. Neurosci.* 20, 1735–1745
74 Huntsman, M.M. and Huguenard, J.R. (2006) Fast IPSCs in rat thalamic reticular nucleus require the GABAA receptor beta1 subunit. *J. Physiol.* 572, 459–475
75 Kanter, E.D. *et al.* (1996) A dendritic GABAA-mediated IPSP regulates facilitation of NMDA-mediated responses to burst stimulation of afferent fibers in piriform cortex. *J. Neurosci.* 16, 307–312
76 Witter, M.P. *et al.* (1988) Entorhinal projections to the hippocampal CA1 region in the rat: an underestimated pathway. *Neurosci. Lett.* 85, 193–198
77 Miles, R. *et al.* (1996) Differences between somatic and dendritic inhibition in the hippocampus. *Neuron* 16, 815–823
78 Tsubokawa, H. and Ross, W.N. (1996) IPSPs modulate spike backpropagation and associated [Ca^{2+}]i changes in the dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* 76, 2896–2906
79 Pearce, R.A. *et al.* (1995) Different mechanisms for use-dependent depression of two GABAA-mediated IPSCs in rat hippocampus. *J. Physiol.* 484, 425–435
80 Mott, D.D. *et al.* (1990) Baclofen facilitates the development of long-term potentiation in the rat dentate gyrus. *Neurosci. Lett.* 113, 222–226
81 Buzsaki, G. (2002) Theta oscillations in the hippocampus. *Neuron* 33, 325–340
82 Bragin, A. *et al.* (1995) Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* 15, 47–60
83 Gray, C.M. and Singer, W. (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* 86, 1698–1702
84 Sejnowski, T.J. and Paulsen, O. (2006) Network oscillations: emerging computational principles. *J. Neurosci.* 26, 1673–1676
85 Winson, J. (1974) Patterns of hippocampal theta rhythm in the freely moving rat. *Electroencephalogr. Clin. Neurophysiol.* 36, 291–301
86 Elfant, D. *et al.* (2008) Specific inhibitory synapses shift the balance from feedforward to feedback inhibition of hippocampal CA1 pyramidal cells. *Eur. J. Neurosci.* 27, 104–113
87 Chapman, C.A. and Lacaille, J.C. (1999) Intrinsic theta-frequency membrane potential oscillations in hippocampal CA1 interneurons of stratum lacunosum-moleculare. *J. Neurophysiol.* 81, 1296–1307
88 Tort, A.B. *et al.* (2007) On the formation of gamma-coherent cell assemblies by oriens lacunosum-moleculare interneurons in the hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* 104, 13490–13495
89 Holsheimer, J. *et al.* (1982) The double dipole model of theta rhythm generation: simulation of laminar field potential profiles in dorsal hippocampus of the rat. *Brain Res.* 235, 31–50
90 Banks, M.I. *et al.* (2000) Interactions between distinct GABA(A) circuits in hippocampus. *Neuron* 25, 449–457
91 Steward, O. and Scoville, S.A. (1976) Cells of origin of entorhinal cortical afferents to the hippocampus and fascia dentata of the rat. *J. Comp. Neurol.* 169, 347–370
92 Colbert, C.M. and Levy, W.B. (1992) Electrophysiological and pharmacological characterization of perforant path synapses in CA1: mediation by glutamate receptors. *J. Neurophysiol.* 68, 1–8
93 Soltesz, I. and Deschenes, M. (1993) Low- and high-frequency membrane potential oscillations during theta activity in CA1 and CA3 pyramidal neurons of the rat hippocampus under ketamine–xylazine anesthesia. *J. Neurophysiol.* 70, 97–116
94 Empson, R.M. and Heinemann, U. (1995) Perforant path connections to area CA1 are predominantly inhibitory in the rat hippocampal–entorhinal cortex combined slice preparation. *Hippocampus* 5, 104–107
95 Kamondi, A. *et al.* (1998) Theta oscillations in somata and dendrites of hippocampal pyramidal cells *in vivo*: activity-dependent phase-precession of action potentials. *Hippocampus* 8, 244–261
96 Csicsvari, J. *et al.* (1999) Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving Rat. *J. Neurosci.* 19, 274–287
97 White, J.A. *et al.* (2000) Networks of interneurons with fast and slow gamma-aminobutyric acid type A (GABAA) kinetics provide substrate for mixed gamma–theta rhythm. *Proc. Natl. Acad. Sci. U. S. A.* 97, 8128–8133
98 Hasselmo, M.E. *et al.* (2002) A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Comput.* 14, 793–817
99 Franks, N.P. (2008) General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat. Rev. Neurosci.* 9, 370–386
100 Banks, M.I. and Pearce, R.A. (1999) Dual actions of volatile anesthetics on GABA(A) IPSCs: dissociation of blocking and prolonging effects. *Anesthesiology* 90, 120–134
101 Gage, P.W. and Robertson, B. (1985) Prolongation of inhibitory postsynaptic currents by pentobarbitone, halothane and ketamine in CA1 pyramidal cells in rat hippocampus. *Br. J. Pharmacol.* 85, 675–681
102 Antkowiak, B. and Heck, D. (1997) Effects of the volatile anesthetic enflurane on spontaneous discharge rate and GABA(A)-mediated inhibition of Purkinje cells in rat cerebellar slices. *J. Neurophysiol.* 77, 2525–2538
103 Lukatch, H.S. and MacIver, M.B. (1997) Voltage-clamp analysis of halothane effects on GABA(A fast) and GABA(A slow) inhibitory currents. *Brain Res.* 765, 108–112
104 Dai, S. *et al.* (2009) Amnestic concentrations of etomidate modulate GABAA,slow synaptic inhibition in hippocampus. *Anesthesiology* 111, 766–773

105 MacIver, M.B. (2009) Abused inhalants enhance GABA-mediated synaptic inhibition. *Neuropsychopharmacology* 34, 2296–2304
106 Collinson, N. *et al.* (2002) Enhanced learning and memory and altered GABAergic synaptic transmission in mice lacking the alpha 5 subunit of the GABAA receptor. *J. Neurosci.* 22, 5572–5580
107 Crestani, F. *et al.* (2002) Trace fear conditioning involves hippocampal alpha5 GABA(A) receptors. *Proc. Natl. Acad. Sci. U. S. A.* 99, 8980–8985
108 Martin, L.J. *et al.* (2009) The physiological properties and therapeutic potential of alpha5-GABAA receptors. *Biochem. Soc. Trans.* 37, 1334–1337
109 Ballard, T.M. *et al.* (2009) RO4938581, a novel cognitive enhancer acting at GABAA alpha5 subunit-containing receptors. *Psychopharmacology (Berl.)* 202, 207–223
110 Howell, O. *et al.* (2000) Density and pharmacology of alpha5 subunit-containing GABA(A) receptors are preserved in hippocampus of Alzheimer's disease patients. *Neuroscience* 98, 669–675
111 Johnston, D. and Brown, T.H. (1983) Interpretation of voltage-clamp measurements in hippocampal neurons. *J. Neurophysiol.* 50, 464–486
112 Spruston, N. *et al.* (1993) Voltage- and space-clamp errors associated with the measurement of electrotonically remote synaptic events. *J. Neurophysiol.* 70, 781–802
113 Williams, S.R. and Mitchell, S.J. (2008) Direct measurement of somatic voltage clamp errors in central neurons. *Nat. Neurosci.* 11, 790–798
114 Golding, N.L. *et al.* (2005) Factors mediating powerful voltage attenuation along CA1 pyramidal neuron dendrites. *J. Physiol.* 568, 69–82
115 Spruston, N. (2008) Pyramidal neurons: dendritic structure and synaptic integration. *Nat. Rev. Neurosci.* 9, 206–221
116 Hausser, M. and Roth, A. (1997) Estimating the time course of the excitatory synaptic conductance in neocortical pyramidal cells using a novel voltage jump method. *J. Neurosci.* 17, 7606–7625
117 Maccaferri, G. *et al.* (2000) Cell surface domain specific postsynaptic currents evoked by identified GABAergic neurones in rat hippocampus *in vitro*. *J. Physiol.* 524, 91–116
118 Jacob, T.C. *et al.* (2008) GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat. Rev. Neurosci.* 9, 331–343
119 Canepari, M. *et al.* (2010) Imaging inhibitory synaptic potentials using voltage sensitive dyes. *Biophys. J.* 98, 2032–2040
120 Cauli, B. *et al.* (2004) Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. *J. Neurosci.* 24, 8940–8949