

Fast and Slow GABAergic Transmission in Hippocampal Circuits



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Overview

Cortical neuronal networks consist of excitatory glutamatergic principal cells (PCs) and GABAergic inhibitory interneurons (INs). Although INs form a minority of the cortical neuron population, they control key aspects of cortical network function by providing feedforward and feedback inhibition, controlling the formation of PC assemblies, defining the excitability of neuronal networks and the timing of the activation of PCs, and promoting synchrony of fast neuronal network oscillations (Freund and Buzsáki 1996; McBain and Fisahn 2001; Klausberger and Somogyi 2008; Sohal 2016; Strüber et al. 2017). INs are highly diverse and can be subdivided into several types on the basis of various criteria, such as intrinsic physiological properties, neurochemical marker content, morphological features, including the laminar distribution of the axon, and finally the postsynaptic target profile of their output (Freund and Buzsáki 1996; Hosp et al. 2014; Savanthrapadian et al. 2014; Yuan et al. 2017). On the basis of synaptic targets, INs have been classified into two major groups, perisomatic- and dendrite-targeting cells.

Transmission at perisomatic GABAergic synapses is characterized by fast time course and large peak amplitudes (Bartos et al. 2001, 2002; Strüber et al. 2015). Fast GABA_A receptor (GABA_AR)-mediated perisomatic inhibition can precisely

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determine the timing and the frequency of action potential discharge in PCs (Cobb et al. 1995; Miles et al. 1996; Pouille and Scanziani 2001). In contrast, inhibitory signaling mediated by dendritic GABAergic contacts has slower time course and shows high degree of diversity (Pearce 1993; Miles et al. 1996; Vida et al. 1998; Banks et al. 1998; Szabadics et al. 2007; Savanthrapadian et al. 2014). The slower time course of dendritic inhibitory (DI) signals is partially due to electrotonic attenuation, when examined in somatic recordings; however, differences in the kinetics of the underlying conductance, as a consequence of differential GABA_AR expression, are likely to contribute significantly. Dendritic inhibition plays a major role in regulating local linear or nonlinear integration of excitatory synaptic inputs, activation of dendritic voltage-gated conductances, synaptic plasticity, and dendritic spike generation (Miles et al. 1996; Makara et al. 2009; Müller et al. 2012). Indeed, recent *in vivo* examinations show that dendritic inhibition is involved in shaping the activity of hippocampal place cells important for spatial navigation (Royer et al. 2012) and certain forms of learning (Lovett-Barron et al. 2014).

In addition to GABA_ARs, metabotropic GABA_BRs mediate a slower form of inhibition by synaptically released GABA (Solís and Nicoll 1992; Isaacson et al. 1993; Scanziani 2000; Booker et al. 2013, 2017b). Activation of GABA_BRs generates a slow inhibitory postsynaptic potential (IPSP) postsynaptically and inhibits transmitter release from the axon terminals presynaptically. Finally, besides these forms of phasic inhibition, extrasynaptic GABA receptors mediate “tonic” inhibition (Nusser and Mody 2002; Scimemi et al. 2005; Glykys and Mody 2006). Tonic inhibition controls the excitability of the cell and the gain in the input-output relationship during synaptic excitation as a function of ambient GABA levels.

In this chapter we review characteristics of GABA_AR-mediated inhibitory transmission at perisomatic and dendritic synapses, as well as GABA_BR-mediated pre- and postsynaptic inhibition in hippocampal networks.

GABA_AR-Mediated Synaptic Inhibition in Hippocampal Circuits

GABA_AR-Mediated Perisomatic Inhibition

A major factor which determines the influence of a given IN on its target cell is the location of the synapses on the surface of the target cell. Inhibitory synapses located close to the soma have a large impact on the generation of action potentials at the output of neurons (Miles et al. 1996; Jonas et al. 2004). These synapses therefore can precisely control timing and frequency of action potentials. Consequently, somanear “phasic” inhibition underlies important cortical network functions such as the synchronization of neuronal activity and the generation of neuronal network oscillations (Cobb et al. 1995; Pouille and Scanziani 2001; Mann et al. 2005; Mittmann et al. 2005; Vida et al. 2006; Doischer et al. 2008). The primary sources of perisomatic

inhibition are basket cells (BCs). These INs show characteristic physiological, pharmacological, and immunohistochemical properties (Freund and Buzsáki 1996; Freund 2003; see also chapter “Morphology of Hippocampal Neurons”). On the basis of the expression profile of Ca^{2+} -binding proteins and neuropeptides, two types of soma-inhibiting cells have been distinguished: parvalbumin (PV)- and cholecystokinin (CCK)-expressing cells (Freund and Buzsáki 1996; Hefft and Jonas 2005; Elgueta et al. 2015). Another IN type, the so-called chandelier or axo-axonic (AA) cells, innervate the axon initial segment of PCs (Somogyi et al. 1985; Soriano et al. 1990; Buhl et al. 1994, 1995), and therefore these INs are in an optimal position to control the initiation of action potentials in their postsynaptic targets. While BCs form synaptic contacts onto both pyramidal cells (PyCs) and other INs, including BCs (Bartos et al. 2001, 2002), AA cells selectively target PCs (Buhl et al. 1994, 1995). The contribution of PV-expressing INs (PV-INs) in neuronal network synchronization has been broadly accepted on the basis of single-unit recordings of PV-INs during spatial exploration demonstrating their strong phase relationship of individual action potentials to single gamma cycles in anesthetized (Tukker et al. 2007; Klausberger and Somogyi 2008) and freely moving rodents (Katona et al. 2014). Moreover, optogenetic approaches allowing light-mediated recruitment of PV-INs or their presynaptic PCs in cortical networks showed that gamma power increased upon PV-IN activation (Cardin et al. 2009; Sohal et al. 2009; Cardin 2016).

PV-BCs GABAergic transmission at PV-BC output synapses is characterized by rapid time course, large peak conductance, and high reliability of transmitter release (Fig. 1; Kraushaar and Jonas 2000; Bartos et al. 2001, 2002; Glickfeld and Scanziani 2006; Glickfeld et al. 2008; Savanthrapadian et al. 2014). Paired whole-cell patch-clamp recordings from presynaptic PV-expressing BCs and postsynaptic PCs in acute hippocampal slices revealed that the time course of unitary GABA_A -mediated inhibitory postsynaptic currents (IPSCs) is extremely fast in all hippocampal areas. In dentate gyrus granule cells (GCs), the rise time (20–80%) is 0.2–0.3 ms, and decay time constant is 3.2–3.5 ms at near-physiological temperatures (Bartos et al. 2002; Table 1).

Highly specialized pre- and postsynaptic mechanisms underlie the rapid time course of unitary IPSCs at PV-BC output synapses. Presynaptically, GABA release is initiated by a brief and precisely timed Ca^{2+} transient. This is reflected by the highly synchronous time course of GABA release at BC-GC synapses (Hefft and Jonas 2005). The high level of synchrony is further realized by the tight coupling of the Ca^{2+} source (P/Q - type Ca^{2+} channels) and the sensor (Bucurenciu et al. 2008). Postsynaptically, fast inhibitory signaling at PV-BC synapses is largely mediated by $\alpha 1$ subunit-containing GABA_A Rs as revealed by postembedding immunogold-labeling studies (Nyíri et al. 2001; Klausberger et al. 2002). Analysis of recombinant GABA_A Rs showed that $\alpha 1\beta 1\gamma 2$ channels deactivate faster than $\alpha 2\beta 1\gamma 2$ channels (Lavoie et al. 1997). Consistent with these findings, bath application of the benzodiazepine type I receptor agonist zolpidem, which has a high affinity to GABA_A Rs containing the $\alpha 1$ subunit (Thomson et al. 2000; Cope et al. 2005), results in a

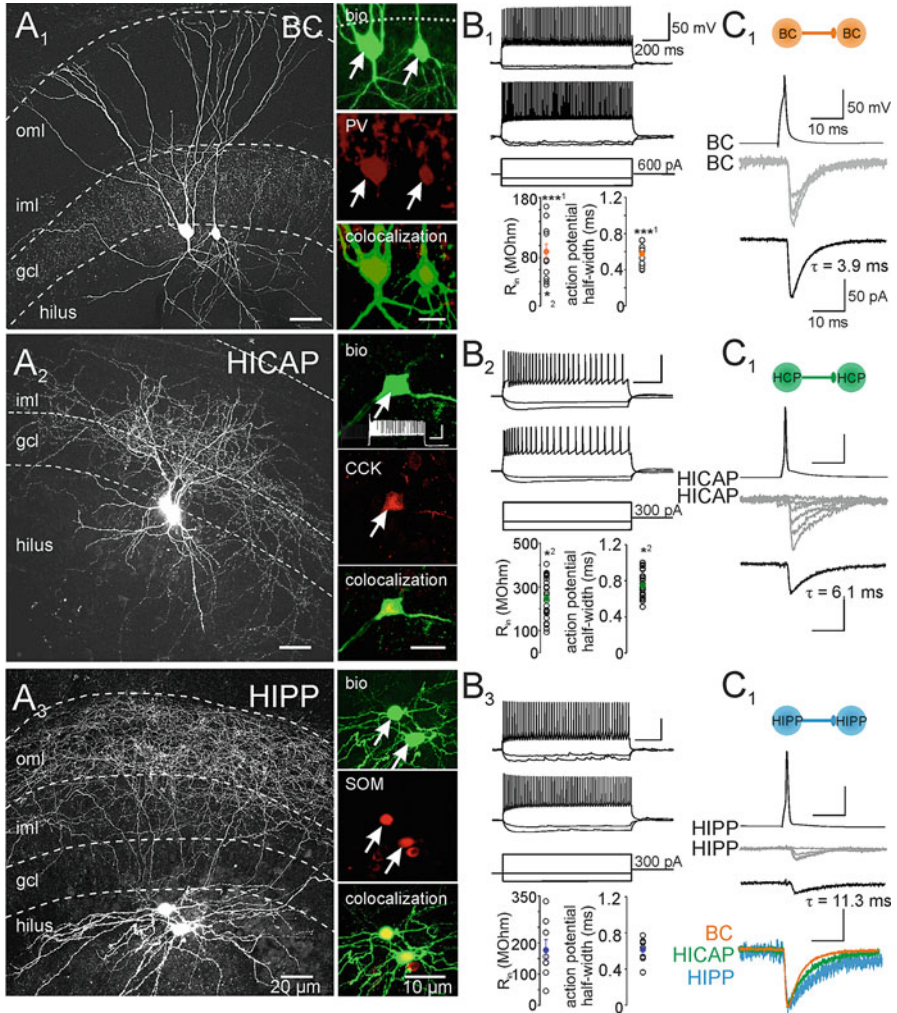


Fig. 1 Morphological, physiological, and synaptic characteristics of perisomatic and dendritic INs in rodent dentate gyrus. **(A)** *left*, confocal image stacks of pairs of synaptically connected GABAergic INs intracellularly labeled with biocytin and visualized with streptavidin conjugated with Alexa Fluor 647 (white labeling). **(A₁)** perisomatic INs with axon in the granule cell layer (gcl). *Right*, basket cells (BCs) are parvalbumin (PV)-positive as revealed by antibody labeling. From top to bottom, green, biocytin labeling, arrows point to both somata; red, PV expression; colocalization of both markers. **(A₂)** commissural-associational path cells (HICAPs) with axon collaterals mainly located in the inner molecular layer (iml). *Right*, a single intracellularly labeled HICAP identified as cholecystikinin (CCK)-positive. Inset, characteristic discharge pattern of the HICAP cell (0.7 nA, 1 s; scale bars, 200 ms, 50 mV). **(A₃)** hilar perforant path-associated cells (HIPPs) with axon located predominantly in the outer molecular layer (oml). *Right*, both neurons co-express somatostatin (SOM; arrows). **(B)** passive and active membrane properties of identified BCs (**B₁**), HICAPs (**B₂**), and HIPPs (**B₃**). Top traces in **B₁–B₃**, voltage trajectories of cell pairs shown in **A** (1 s, –100, –50, 300–800 pA). Summary graphs in **B₁–B₃** show *left* the input resistance

marked prolongation of the decay time constant of PV-BCs IPSCs (Thomson et al. 2000; Doischer et al. 2008).

The peak amplitude of the inhibitory conductance at PV-BC output synapses shows considerable variability across hippocampal areas (Table 1). Nevertheless, peak amplitudes are generally high (up to 9.5 nS), which can be explained by the large number of synaptic contact sites between the coupled neurons. In the CA1 area, for example, the number of contacts per unitary connection is between 10 and 12 (Buhl et al. 1995). Consistent with the high number of contact sites, the failure rate of transmission is low (Hefft and Jonas 2005; Doischer et al. 2008; Table 1). The reliable transmission at BC output synapses is further supported by the high initial probability of transmitter release, estimated to be 0.79 in the dentate gyrus (Kraushaar and Jonas 2000).

BC synapses display differences in kinetic properties depending on the identity of the postsynaptic target (Bartos et al. 2001, 2002; Doischer et al. 2008). In particular, the decay time constant was found to be by a factor of ~ 2 faster in postsynaptic BCs than in PCs. The mean value of the decay time constant at BC-BC pairs in the dentate gyrus, CA1, and CA3 are 2.5, 1.7, and 1.2 ms, respectively (Bartos et al. 2001, 2002; Table 1). These target cell-specific differences in the hippocampus (Bartos et al. 2002; Glickfeld et al. 2008) could be explained by the expression of distinct postsynaptic GABA_ARs. PV-BCs express $\alpha 1$ GABA_AR subunits at higher levels than PCs (Gao and Fritschy 1994; Fritschy and Möhler 1995; Klausberger et al. 2002). Interestingly, however, other parameters of the synapses, including the rise time, the peak amplitude of the inhibitory conductance, and the failure rate of synaptic transmission, show no differences between BC-BC and PV-BC-PC synapses (Bartos et al. 2001 2002; Table 1).

Previous paired recordings have been performed between two closely spaced neurons due to the high connectivity among closely spaced cells. Recent investigations, however, indicate that the amplitude and time course of perisomatic inhibition depends on the axonal distance between the pre- and postsynaptic neuron (Strüber et al. 2015, 2017). In particular in the dentate gyrus, PV-INs effectively control the activity of large neuron populations by their wide axonal arborization. Here, synaptic signals become weaker with axonal distance between presynaptic BC and its target GC due to lower contact numbers. The decay of uIPSCs also declines more slowly with distance, resulting from changes in GABA_AR subunit



Fig. 1 (continued) (R_{in}) of the recorded cell types and *right* the half duration of single action potentials. Each circle represents a single data point, and colored circles with lines represent mean values \pm SEM. **C**, unitary IPSCs (uIPSCs) recorded at pairs shown in **A**. A presynaptic action potential (top) evokes uIPSCs in the postsynaptic cell. Single uIPSCs (6 traces) are shown superimposed (middle), and the average uIPSC (30 traces) at -70 mV is depicted below. Schematic illustration represents the recorded neuron types; In *C3bottom*, average uIPSCs shown in *C1-C3* were peak normalized and superimposed. *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$; 1, significantly different to HICAP; 2, different to HIPP. (Adapted from Savanthrapadian et al. 2014; with permission, © The Society for Neuroscience)

Table 1 Kinetic properties of perisomatic inhibition

Postsynaptic cell type	Rise time (ms)	Decay τ (ms)	Peak conductance (nS)	Failure rate (%)	Paired recording configuration	Publication
DG						
GC	0.2–0.3 ^a /0.5 ^{ad}	3.4–6.5/14–22 ^d	2.0–6.8/1.7 ^{cd}	<7		
	0.2 \pm 0.03 ^a	3.4 \pm 0.4	2.0 ^c	5.5 \pm 4.0	PV + BC-GC	Bartos et al. (2002)
		5.2			BC-GC	Bartos et al. (2001)
	0.26 \pm 0.01 ^a	6.5	6.8 ^c	6.5 \pm 1.0	BC-GC	Kraushaar and Jonas (2000)
	0.53 \pm 0.04 ^{ad}	20.0 \pm 1.1 ^d		0.5 \pm 0.3 ^d	BC-GC	Hefft and Jonas (2005)
		4.4 \pm 0.5	3.7 ^c	2 \pm 2	BC-GC	Doischer et al. (2008)
	0.46 \pm 0.03 ^{ad}	13.6 \pm 0.8 ^d			Fast-spiking IN-GC	Liu et al. (2014)
GC	0.87	20.1^d		18.6^d		
	0.87 \pm 0.08 ^d	20.1 \pm 0.8 ^d		18.6 \pm 6.3 ^d	CCK-IN-GC	Hefft and Jonas (2005)
BC	0.3–0.4^b	2.5–3.9	2.3–3.5^c	2–11		
	0.3 \pm 0.02 ^a	2.5 \pm 0.2		10.5 \pm 5.5	BC-BC	Bartos et al. (2001)
	0.3 \pm 0.03 ^a	2.5 \pm 0.4	2.29 ^c	5 \pm 3	PV + BC-BC	Bartos et al. (2002)
		2.0 \pm 0.2	2.5 ^c	4.5 \pm 3	BC-BC	Doischer et al. (2008)
	0.4 \pm 0.06 ^a	3.9 \pm 0.2	3.5 ^c	1.7 \pm 1.7	BC-BC	Savanthrapadian et al. 2014
DI cell	0.2	4.0	3.1	11		
	0.23 \pm 0.04	3.95 \pm 0.75	3.06	10.8 \pm 6.3	BC-DI	M. Bartos unpublished

CA3									
PC	1.1–0.3^a	3.3–4.6	2–8^c	<17					
	0.3 ± 0.02 ^a	3.3 ± 0.1	5.27 ^c	0		PV + BC-PC		Bartos et al. (2002)	
	1.2 ± 0.1 ^b		5.2 ^c	5.6 ± 2.5		Fast-spiking BC-PC		Szabó et al. (2010)	
	1.1 ± 0.1 ^b	11.0 ± 0.6 ^d	8.8 ^c	1.6 ± 1.1		Axo-axonic-PC		Szabó et al. (2010)	
	1.8 ± 0.3 ^b		2 ^c	16.8 ± 2.9		Regular spiking BC-PC		Szabó et al. (2010)	
BC	0.25^a	1.2	3.9^c	10					
	0.25 ± 0.02 ^a	1.2 ± 0.02	3.94 ^c	10 ± 10		PV + BC-BC		Bartos et al. (2002)	
CA1									
PC	0.3–0.7^a0.66–0.86^b	3.5–8.3	1.6–9.5	3–35					
	0.3 ± 0.02 ^a	3.5 ± 0.5	9.53 ^c	3 ± 2		PV + BC-PC		Bartos et al. (2002)	
	0.66 ± 0.06 ^b	7.03 ± 1.03	2.07			Fast-spiking BC-PC		Glickfeld et al. (2008) and Glickfeld and Scanziani (2006)	
	0.86 ± 0.09 ^b	8.3 ± 1.22	1.61			Regular spiking BC-PC		Glickfeld et al. (2008) and Glickfeld and Scanziani (2006)	
	0.73 ± 0.05 ^b	6.8 ± 0.2	3.12 ^c	35 ± 7		CCK + BC-PC		Neu et al. (2007)	
	0.7 ± 0.2	7.1 ± 1.2				CCK + BC-PC		Tyan et al. (2014)	
BC	0.3^a	1.7	5.1^c	4					
	0.27 ± 0.02 ^a	1.7 ± 0.1	5.12 ^c	4 ± 3		PV-GFP + BC-BC		Bartos et al. (2002)	

Abbreviations: *PC* pyramidal cell, *PV* parvalbumin, *BC* basket cell, *CCK* cholecystokinin, *MFA* mossy fiber-associated cell, *DI cell* dendrite-inhibiting cell
^a20–80% rise time, ^b10–90% rise time, ^ccalculated from peak IPSC and estimated Cl⁻ reversal potential, ^drecorded at room temperature (22 ± 2°C)

composition (Strüber et al. 2015). Indeed, antibody labeling revealed that closely spaced GCs are contacted by BC-mediated GABAergic synapses expressing less $\alpha 2$ subunits postsynaptically, whereas the $\alpha 2$ content increases at more distant target GC (Strüber et al. 2015). Interestingly, this form of distance-dependent perisomatic inhibition was independent of the target cell and observed at both postsynaptic GCs as well as PV-INs (Strüber et al. 2017).

Morphological analysis revealed that many BC-IN synapses are on proximal apical dendrites because the cell body of these cells is often located below the somatic layer. The dendritic position of the synapses leads to attenuation and deceleration of the synaptic current (Johnston and Brown 1983; Rall and Segev 1985; Major et al. 1993; Doischer et al. 2008). Therefore, to determine the real-time course of the inhibitory conductance, rise and decay time constants of the inhibitory postsynaptic conductance were estimated using passive cable models of reconstructed BC-IN pairs (Bartos et al. 2001). In these simulations, the mean value for the 20–80% rise time was found to be 0.17 ± 0.04 ms and the decay time constant 1.8 ± 0.6 ms (Bartos et al. 2001). These values were by a factor of 1.8 and 1.4 faster than the experimentally obtained ones, indicating a considerable electrotonic deceleration of the evoked IPSCs for these proximally positioned dendritic synapses.

CCK-BCs Information on kinetic properties, synaptic strength, and precision in transmitter release at CCK-BC inhibitory output synapses is limited (Table 1). Paired whole-cell patch-clamp recordings showed that uIPSCs at CCK-BC to PC synapses in CA1 have a 10–90% rise time of 0.73 ± 0.05 ms and a decay time constant of 6.8 ± 0.2 ms (Neu et al. 2007), indicating that synaptic inhibition at CCK-BC output synapses might be slower than at PV-BC output synapses (Bartos et al. 2002). Furthermore, paired recordings at CCK-BC to GC synapses in the dentate gyrus revealed average uIPSCs with slow 20–80% rise times and decay time constants (~ 0.9 ms and ~ 22 ms, respectively; Table 1; Harney and Jones 2002; Hefft and Jonas 2005). However, these recordings have been performed at room temperature (20–22 °C) and therefore cannot be directly compared with data obtained at PV-BC output synapses measured at near-physiological temperatures (Bartos et al. 2002). While PV-BCs display a fast-spiking (FS) discharge pattern, CCK-BCs have been shown to be regular-spiking (RS) (Freund 2003). Whole-cell recordings of presynaptic RS-BCs and postsynaptic PCs in CA1 revealed uIPSCs with moderately fast time course with a 10–90% rise time of 0.86 ± 0.09 ms and a decay time constant of 8.3 ± 1.22 ms (Table 1; Glickfeld and Scanziani 2006, Glickfeld et al. 2008). These values were, however, not significantly different to the ones obtained at FS-BC to PCs synapses with a 10–90% rise time of 0.66 ± 0.06 ms and a decay time constant of 7.03 ± 1.03 ms in the same experiments (Table 1; Glickfeld and Scanziani 2006; Glickfeld et al. 2008). Although the time course of IPSCs at FS and RS output synapses are not significantly different, they seem to be mediated by different postsynaptic GABA_AR subunits. Putative CCK/vasoactive intestinal polypeptide (VIP)-immunopositive BC synapses show several-fold lower $\alpha 1$, but higher $\alpha 2$ subunit content than PV-positive synapses (Nyíri et al. 2001;

Klausberger et al. 2002). Finally, CCK-IN to GC synapses show a higher level of transmission failures than PV-BC to GC synapses, pointing to major differences in the release probability among the two BC types (Table 1).

In addition to differences in the kinetics, strength, reliability, and transmitter release at CCK-IN output synapses are characterized by a marked asynchrony (Maccaferri et al. 2000; Hefft and Jonas 2005; M. Bartos, unpublished observation). The less precisely timed GABA release results in a slow rise time of unitary IPSCs observed at CCK-IN to principal cell synapses in the dentate gyrus and CA1 (Maccaferri et al. 2000; Hefft and Jonas 2005). The standard deviation of the first latency distribution, which can be used as a measure for synchrony of release, is significantly larger at CCK-IN to GC than at PV-BC to GC synapses (CCK-INs: 0.95 ± 0.3 ms versus 0.26 ± 0.06 ms). In summary, the properties of the inhibitory output differ markedly between CCK- and PV-BCs. While PV-BC output synapses are characterized by fast, strong, precisely timed transmission, CCK-BC synapses are slower, are weaker, and show asynchronous signaling.

Similar to PV-BCs, CCK-BCs do also target other INs including CCK-BCs. While neuroanatomical studies indicate that the mutual connectivity is comparable to that of PV-BCs, and the total inhibitory input is stronger (Mátyás et al. 2004), functionally, perisomatic inhibition appears to be weaker in CCK-INs. Recordings from the two types in the CA1 area revealed that IPSCs evoked by minimal stimulation in the cell body layer had large peak amplitudes in PV-immunopositive cells, but small in CCK-BCs (Glickfeld et al. 2008). In comparison to IPSCs recorded simultaneously in PyCs, the ratio of the amplitudes was close to 1 in PV- but only 0.14 ± 0.05 in CCK-BCs, pointing to a target cell-dependent difference in the strength perisomatic inhibition (Glickfeld et al. 2008).

Although HICAPs of the dentate gyrus do not have the classical axonal arbors as BCs located in the GC layer, they are CCK-positive (Savanthrapadian et al. 2014), giving rise to the hypothesis that dentate gyrus CCK-expressing BCs are homologous to HICAP cells.

Chandelier or Axo-Axonic (AA) Cells In contrast to PV-BCs, information on the functional properties at AAs output synapses is scarce. Data from paired recordings in the dentate gyrus showed that these INs evoke fast GABA_AR-mediated IPSPs in GCs (Buhl et al. 1994). Properties of the currents underlying the effect of AAs were examined in paired whole-cell patch-clamp recordings in the CA3 area. Results showed that unitary AA IPSCs have larger amplitude (463.3 ± 61.8 pA) and a moderately fast time course (rise time, 1.1 ± 0.1 ms; decay time constant 11.0 ± 0.6 ms at room temperature; Szabó et al. 2010). Recordings from neocortical AA cells and synaptically coupled PyCs suggested that the effect of this IN type is not inhibitory but excitatory (Szabadics et al. 2006). Results from the hippocampus, however, indicate that AA cells predominantly mediate hyperpolarization in the postsynaptic PC population (Glickfeld et al. 2009). Indeed, a hyperpolarizing effect of GABAergic synapses located at the AA segment controls ectopic backpropagation of action potentials in PC axons and thereby lowers the invasion of the soma by

antidromic action potentials to maintain the functional polarization of PCs during network oscillations (Dugladze et al. 2012).

Dynamic Properties of Perisomatic Inhibition When two action potentials are elicited in the presynaptic BC in short succession, the amplitude of the second IPSC elicited in the postsynaptic cell is smaller than that of the first. This phenomenon is called paired-pulse depression (PPD) (Kraushaar and Jonas 2000; Bartos et al. 2001 2002). Coefficient of variation analysis (Malinow and Tsien 1990) suggests a presynaptic locus for PPD (Bartos et al. 2001). In fact, PPD is independent of the identity of the postsynaptic neuron: the extent of PPD of PV-BCs evoked ISPCs was found to be similar at in PV-BC and PCs (~31 % and ~33 %, respectively; Bartos et al. 2002). Under conditions of prolonged activity, synaptic transmission at BC-BC and BC-GC synapses show rapid and marked initial depression but subsequently stabilize at a lower level (Kraushaar and Jonas 2000; Bartos et al. 2001) demonstrating that GABAergic transmission is extremely stable at BC output synapses.

CCK-BC output synapses express PPD to a similar extent as PV-BCs in the dentate gyrus (Hefft and Jonas 2005). During repetitive stimulation (10 action potentials, 50 Hz), however, the onset of depression was slower at CCK-BCs than at PV-BCs (Hefft and Jonas 2005). Interestingly, in the CA3 and CA1 area high-frequency trains elicited in CCK-BCs result in facilitation of IPSCs in PCs (Losonczy et al. 2004; Földy et al. 2006; Neu et al. 2007). Release at these synapses is tightly controlled by endocannabinoids through CB1 receptors resulting in a low release probability when the cells are quiescent (Földy et al. 2006).

Dendritic GABA_AR-Mediated Inhibition

Dendritic inhibition is mediated by a highly heterogeneous population of INs. Some of these INs, such as neurogliaform cells (NGFCs), perforant path- and Schaffer collateral-associated INs of the CA1 area, or MOPP cells of the dentate gyrus, mediate exclusively feedforward inhibition (Vida et al. 1998; Price et al. 2008; Elfant et al. 2008); others, such as O-ML and HIPP INs, provide feedback inhibition (Han et al. 1993; Blasco-Ibáñez and Freund 1995); and yet another group, such as CA1 bistratified cells, are involved in both types of inhibitory microcircuits. Dendritic inhibition controls excitation of cells by glutamatergic inputs, voltage-dependent activation of NMDA receptors, and synaptic plasticity (Staley and Mody 1992; Davies et al. 1991; Mott and Lewis 1991; Miles et al. 1996). Furthermore, dendritic inhibition modulates the activation of voltage-gated channels, the generation of slow Ca²⁺ spikes, and the backpropagation of action potentials (Miles et al. 1996; Buzsáki 1996).

The large electrotonic distance between synapse location and the site of somatic action potential generation, as well as the low-pass filtering properties of passive membranes will result in attenuation of synaptically evoked IPSCs (Johnston and

Brown 1983; Rall and Segev 1985; Major et al. 1993; Häusser and Roth 1997). Dendritic inhibition will thereby have a slower, tonic rather than fast, “phasic” inhibitory effect at the soma. Thus, in contrast to perisomatic inhibition which determines spike timing and synchronizes the activity of PCs, dendritic inhibition may offset the input-output relation of postsynaptic target cells (Mitchell and Silver 2003).

Information on the functional properties of GABAergic transmission of identified DIs is limited. The following section summarizes data on properties of GABA_AR-mediated transmission at the output synapses of morphologically-identified DIs from the CA1 and the dentate gyrus available in the literature (Hosp et al. 2014; Savanthrapadian et al. 2014).

Neurogliaform Cells NGFCs form a dense axonal plexus in the *stratum (str.) lacunosum-moleculare* of CA1 (Vida et al. 1998; Price et al. 2005, 2008) and the molecular layer (Armstrong et al. 2011). GABA_AR-mediated inhibitory signaling at NG output synapses is characterized by slow time course and small peak amplitude (Price et al. 2005, 2008; Szabadics et al. 2007; Armstrong et al. 2011). Paired whole-cell patch-clamp recordings of presynaptic NGFCs and postsynaptic PCs in acute hippocampal slice preparations at near-physiological temperature (30–34 °C) revealed a decay time constant of the unitary IPSCs of 50 ± 4.9 ms and an underlying peak conductance of ~ 0.48 nS (Table 2; Price et al. 2008). Similarly, paired recordings of synaptically interconnected NGFCs showed slow kinetics with an average decay time constant of 42.05 ± 21.03 ms (Table 2; Price et al. 2005). NGFCs additionally communicate with other types of INs, thereby forming networks of synaptically connected GABAergic cells. Inhibition at these NGFC to non-NGFC synapses is also characterized by a long decay time constant (37.4 ± 11.86 ms; Table 2; Price et al. 2005). In the dentate gyrus, faster kinetics have been observed at NGFCs targeting GCs, but they were still slower than at BC-GC synapses with a rise time (10–90%) of 5.8 ± 1.1 ms, an amplitude of 8.01 ± 1.22 pA ($V_{\text{hold}} -50$ mV), and a decay time constant of 14.7 ± 3.6 ms (Armstrong et al. 2011). Thus, synaptic inhibition by NGFCs has a very slow time course, independent of the nature of the target cell, suggesting that this neuron type is the source of the slow dendritic inhibition observed in earlier studies (Pearce 1993; Banks et al. 1998). The slow time course of the inhibitory conductance stems from several structural and functional characteristics, including spillover of GABA from the synapses formed by the dense axonal arbor and the properties of the GABA receptors on the postsynaptic membrane (Szabadics et al. 2007).

The dynamic properties of GABAergic transmission at NGFC output synapses during repetitive presynaptic activation were characterized by a marked depression (5 Hz trains of 4 presynaptic action potentials). The peak amplitude of the second IPSC in such a train of presynaptic activity was reduced by $\sim 40\%$ at NGFC to PyC synapses (Price et al. 2008) and by $\sim 25\%$ at NGFC-NGFC synapses (Price et al. 2005). Thus, GABA release at NGFC output synapses is strongly depressing.

Table 2 Kinetic properties of dendritic inhibition

Postsynaptic Cell type	20–80 % rise time (ms)	Decay τ (ms)	Peak conductance (nS)	Failure rate (%)	Paired recording configuration	Publication
DG						
GC	0.6/0.9–1.1^a	6.1/20.1–25.4^a	1.5/1.1^a	32/19–65^a		
	0.56 \pm 0.13	6.1 \pm 1.7	1.50	31.5 \pm 8.3	DI-GC	M. Bartos (unpublished)
		24.0 \pm 1.0 ^a	1.12 ^a	65 \pm 5 ^a	HICAP-GC	Harney and Jones (2002)
	0.87 \pm 0.08 ^a	20.1 \pm 0.8 ^a		18.6 \pm 6.3 ^a	HICAP-GC	Hefft and Jonas (2005)
	1.11 \pm 0.08 ^a	25.4 \pm 2.1 ^a			Non fast-spiking cells-GC	Liu et al. (2014)
BC	0.7	5.5	0.6–1.5	48		
	0.70 \pm 0.15	5.9 \pm 1.7	0.84	40.5 \pm 10.7	DI-BC	M. Bartos (unpublished)
	0.69 \pm 0.06	5.5 \pm 0.3	0.61 ^b	48.3 \pm 5.3	HICAP-BC	Savanthrapadian et al. (2014)
	0.7 \pm 0.1	5.5 \pm 0.6	1.54 ^b		HIPP-BC	Savanthrapadian et al. (2014)
HICAP	0.7	6.4	0.32	57		
	0.4 \pm 0.18	5.3 \pm 1.01	0.46		HICAP-HICAP	M. Bartos (unpublished)
	0.7 \pm 0.09	6.4 \pm 0.8	0.32 ^b	57.2 \pm 6.5	HICAP-HICAP	Savanthrapadian et al. (2014)
HIPP	0.5	10.9	0.62	50		
	0.5 \pm 0.08	10.9 \pm 1.9	0.62 ^b	50.4 \pm 6.1	HIPP-HIPP	Savanthrapadian et al. (2014)
NG	5.8; 10–90%	14.7	8.01	50		
	5.8 \pm 1.1	14.7 \pm 3.6	8.01 \pm 1.22 ^b	–	NG-GC	Armstrong et al. (2011)

CA1								
PC		50		0.11^b				
		50 ± 4.9		0.11 ^b		NG-PC		Price et al. (2008)
NG		42		0.48^b				
		42.05 ± 21.03		0.48 ^b		NG-NG		Price et al. (2005)
		37.4 ± 11.86				NG- to non-NG		Price et al. (2005)
SO-IN		1.3–6.2		0.43–1.3				
		9–23		5–60				
		23.0 ± 5.0		1.34	5 ± 4	O-LM-IN to SL-IN		Elfant et al. (2008)
		6.2 ± 0.6		0.43		O-LM-IN to PC		Maccaferri et al. (2000)
		1.3 ± 0.1			59.7 ± 6.0	IS3 to O-LM		Tyan et al. (2014)
SLM-IN		10						
		10.2 ± 6.6				SLM-IN to NG		Price et al. (2005)
CA3								
MFA-IN		0.3–0.9		5.0				
		4.7		36–100				
		0.28 ± 0.08		4.97 ^b		MFA-IN-PC		Vida and Frotscher (2000)
		0.9 ± 0.08			96–100/0.2 Hz	MFA-IN-PC		Losonezy et al. (2004)
		4.8 ± 0.3			36 ± 5/25 Hz			

Abbreviations: PC pyramidal cell, NGC neurogliaform cell, SL stratum lucidum, IN interneuron, DI cell dendrite-inhibiting cell
^aRecorded at room temperature (21–24°C); ^bCalculated from peak IPSC and estimated Cl⁻ reversal potential

Stratum Oriens Interneurons (SO-IN) Functional synaptic communication has been identified between CA1 INs with their somata and dendrites in *str. oriens* and postsynaptic PCs. SO-INs are highly diverse, but one of the most abundant types is the so-called oriens lacunosum-moleculare (O-LM) IN with axonal projection to the *str. lacunosum-moleculare* (Maccaferri et al. 2000). Electron microscopy revealed that the axon terminals of O-LM cells form symmetrical synapses with the distal apical dendrites, mainly shaft, but also dendritic spines, of PyCs and other INs (Gulyás et al. 1993; Sik et al. 1995; Katona et al. 1999). Unitary IPSCs originating from O-LM cells and recorded at the soma of postsynaptic PCs at near-physiological temperature (~ 30 °C) have small peak amplitudes (~ 0.43 nS) and slow time courses with a 10–90% rise time of 6.2 ± 0.6 ms and a decay time constant of 20.8 ± 1.7 ms (Table 2; Maccaferri et al. 2000). These dendritic inputs are markedly slower than perisomatic inhibitory synapses, but considerably faster than “slow” dendritic inhibition mediated by NGFCs.

Similarly to O-LM to PC connections, GABA_AR-mediated inhibition between presynaptic O-LM and postsynaptic SL-INs is slow and weak with a decay time constant of 23 ± 5 ms and a peak conductance of 1.34 nS (Table 2, Elfant et al. 2008). Short-term plasticity was characterized by $\sim 40\%$ PPD at 100 ms inter-spike intervals. Finally, paired-pulse modulation resulted always in synaptic depression independent of the type of the postsynaptic IN (Elfant et al. 2008). In contrast, similar activity patterns failed to influence the second IPSC in PyCs ($93 \pm 4\%$; Maccaferri et al. 2000), raising the possibility of target cell-specific differences in presynaptic properties of these synapses.

Interneuron-Specific Cells (IS-3) IS-3 cells co-express the VIP and calretinin in the hippocampal area CA1 and are located with their soma in the *str. oriens/alveus* (O/A). They innervate several O/A INs including O-LM, bistratified cells, BCs, and oriens-oriens INs with preferential innervation of O-LM cells through dendritic synapses (Tyan et al. 2014). The amplitude of uIPSCs was small and the time course slow with low release probability (Table 2), which was reflected in a high failure rate (59.7%). An O-LM cell was contacted by an IS-3 cell via multiple contact sites. Recruitment of converging inhibitory inputs from IS-3 cells onto target O-LM neurons controlled their firing rate and the timing of action potential generation, indicating that dendritic inhibition provided by IS-3 cells is required for precise activity-dependent recruitment of O-LM cells and thus feedback inhibition in the network.

Mossy Fiber-Associated Interneurons (MFA) MFA INs have dense axonal arborization co-aligned with mossy fibers (MFs) in the *str. lucidum* of CA3 and the hilus (Vida and Frotscher 2000). Their dendrites are located in the *strata radiatum and oriens*, indicating that these INs are innervated by associational and commissural fibers and thus primarily mediate feedback inhibition. Output synapses of MFA INs are found on proximal dendritic shafts and to a lesser degree on somata of PyCs. IPSCs recorded at postsynaptic PCs had fast 20–80% rise times of 0.28 ± 0.08 ms and decay time constants of 4.6 ± 1.2 ms (Vida and Frotscher 2000; Losonczy

et al. 2004; Table 2). The unitary peak conductance was high with an estimated 5 nS. Thus, in comparison to other DIs, GABAergic transmission at MFA output synapses is characterized by fast time courses and high strength. Dynamic properties of MFA synapses are similar to CCK-BCs in that they have a low initial release probability, show a remarkable frequency-dependent facilitation, and transmit with high reliability during high-frequency trains (Vida and Frotscher 2000; Losonczy et al. 2004).

Dendritic Inhibitory Interneurons in the Dentate Gyrus The dense layer-specific axonal distribution of the various DI cells indicates the formation of GABAergic synapses located on the entire somato-dendritic domain of INs and PCs in the dentate gyrus (Han et al. 1993; M. Bartos, unpublished data). Unitary inhibitory events elicited by the activation of DI cells recorded at the soma of GCs and INs are slower and weaker than perisomatic inhibition (Fig. 1; Savanthrapadian et al. 2014). The difference is in part due to electrotonic attenuation of the synaptic events, but properties of postsynaptic GABA_ARs are likely to be of different subunit composition (Table 2). Paired recordings of presynaptic DIs and postsynaptic target cells at near-physiological temperature (32–34 °C) revealed unitary IPSCs with the following parameters:

uIPSCs at HICAP-HICAP synapses were induced after a 1.8-fold longer synaptic latency (2.2 ± 0.1 ms) with a 10.9-fold smaller peak amplitude (12.9 ± 3.9 pA vs. BC-BC in mice 140.2 ± 30.8 pA) and slower time course (rise time 0.7 ± 0.09 ms, decay 6.4 ± 0.8 ms). The coefficient of variation (CV) in the synaptic latency was three times higher at HICAP-HICAP than BC-BC synapses (0.43 ± 0.08 vs. 0.14 ± 0.007). However, the decay time constant of the unitary IPSCs is slower (3.95 ± 0.75 ms) than at BC-BC synapses (2.5 ± 0.2 ms). Similarities in the functional synaptic properties are also evident between BC-BC and HIPP-HIPP connections. Inhibitory signals at HIPP-HIPP synapses are evoked after a similar mean synaptic latency (1.5 ± 0.16 ms) with a low CV (0.2 ± 0.04). The rise time of uIPSCs is also short (0.5 ± 0.08 ms) similar to BC-BC paired recordings, indicating a highly synchronous GABA release. Some differences in the synaptic signaling are also apparent. First, the percentage of failures is 29.7-fold higher than at BC-BC synapses ($50.4 \pm 6.1\%$). Second, the amplitude of uIPSCs was 5.6 times smaller (25.0 ± 11.3 pA) than at BC-BC synapses. Finally, the decay is 2.8-fold slower (10.9 ± 1.9 ms).

Although HIPP cells project their main axonal arbors to the outer molecular layer of the dentate gyrus, some axon fibers are located in the hilus. Indeed, the short latency at HIPP-HIPP signaling can be explained by the synapse location close to the soma of the target cell as revealed by single-cell reconstructions (Savanthrapadian et al. 2014). HICAP-HICAP pairs with axon collaterals in the inner molecular layer form their contact sites at apical dendrites (Savanthrapadian et al. 2014). During trains of 10 action potentials at 50 Hz, HICAP-HICAP synapses express multiple-pulse facilitation (MPF) with a mean $uIPSC_{10}/uIPSC_1$ ratio of 1.6 ± 0.4 . Signals at HIPP-HIPP synapses have a biphasic response with an initial

strongly facilitating phase (uIPSC₅/uIPSC₁ ratio 2.4 ± 0.3) followed by a second phase characterized by a decline in subsequent uIPSC size (uIPSC₁₀/uIPSC₁ ratio 1.4 ± 0.5 ; Savanthrapadian et al. 2014).

Reversal Potential (E_{syn}) of Synaptically Evoked IPSCs

Several lines of evidence indicate that GABA_AR-mediated synaptic inhibition on mature INs is not hyperpolarizing as previously assumed but “shunting” (Alger and Nicoll 1979; Andersen et al. 1980; Martina et al. 2001; Chavas and Marty 2003; Vida et al. 2006). Shunting inhibition is defined as an inhibitory effect, which only minimally affects the membrane potential, but counteracts excitation by short-circuiting the underlying currents. In this scenario, the reversal potential of synaptically evoked IPSCs (E_{syn}) is close to the resting membrane potential (V_{rest}), e.g., in the voltage range between V_{rest} and the threshold for action potential generation (Bartos et al. 2007; Sauer et al. 2012). To determine E_{syn} , whole-cell recordings from BCs were performed in the perforated-patch configuration in the dentate gyrus of rats and PV-EGFP-expressing mice (Vida et al. 2006). The ionophore gramicidin preserves the intracellular Cl⁻ concentration during recording, thus allowing a realistic assessment of E_{syn} (Kyrozos and Reichling 1995). To determine E_{syn} , IPSCs were evoked by extracellular stimulation in the PC layer at varying holding potentials. Synaptically evoked IPSCs reversed on average at -52 ± 1.9 mV (Vida et al. 2006). This value was more positive than the corresponding V_{rest} of -58.4 ± 1.4 mV, but more negative than the threshold potential (Table 3), indicating that inhibition is shunting in BCs. Similarly, perforated-patch recordings from CA3 *str. pyramidale*, *str. oriens*, and *str. lucidum* INs revealed that GABA_AR-mediated synaptic inhibition is shunting or slightly hyperpolarizing with average E_{syn} values 4–5 mV more positive than the corresponding V_{rest} (Table 3; Lamsa and Taira 2003; Banke and McBain 2006). These results have been further confirmed in CA1 *str. radiatum* INs by using cell-attached recordings of GABA_AR-mediated effects (E_{syn} : -69.1 ± 1 mV; V_{rest} : -66 ± 1 mV; Tyzio et al. 2008).

In contrast to INs, E_{syn} of synaptically evoked IPSCs in PCs seems to be diverse (Table 3). Synaptic inhibition in GCs is shunting with an E_{syn} ~ 1 – 10 mV more positive than the resting membrane potential (Table 3, Overstreet-Wadiche et al. 2005; Sauer et al. 2012). Noninvasive recording of unitary field potentials which reflect the postsynaptic effect of GABA release from an identified presynaptic BC confirmed the shunting nature of perisomatic inhibition in the dentate gyrus (Sauer et al. 2012). Importantly, these results did not depend on the age of the animal, excluding a late developmental change in E_{syn} at this synapse (Sauer et al. 2012). Synaptically evoked IPSCs in CA3 PCs reverse at ~ -73 mV, which is ~ 10 mV more negative than the corresponding V_{rest} of ~ -63 mV (Table 3), reflecting hyperpolarizing inhibition in these neurons (Banke and McBain 2006; Lamsa and Taira 2003). In contrast, somatic cell-attached recordings from CA3 PyCs reveal shunting or even depolarizing inhibition with an E_{syn} of -75.3 ± 0.9 mV and a

Table 3 Reversal potential of GABAergic responses

Cell type	E_{syn} (mV)	V_{rest} (mV)	Gramicidin perforated-patch recording technique	Publication
DG				
GC	-72/-74-82 ^a	-75 ^a		
	-71.9 ± 1.9		Synaptic stimulation	Kraushaar and Jonas (2000)
	-74 ± 7 ^a	75 ^b	Synaptic stimulation	Overstreet-Wadiche et al. (2005)
	-81.6 ± 2.2 ^a		GABA bath application	Tozuka et al. (2005)
	-64.5 ± 2.4	-75.8 ± 1.1	Synaptic stimulation	Sauer et al. (2012)
BC	-57/-52 ^a	-64/-58 ^a		
	-52.3 ± 1.9 ^a	-58.4 ± 1.4 ^a	Synaptic stimulation	Vida et al. (2006)
CA3				
PC	-73-75	-63-78		
	-72.7 ± 0.9	-64.6 ± 0.8	Synaptic stimulation	Lamsa and Taira (2003)
	-73 ± 3.8	-62.8 ± 4.4	Synaptic stimulation	Banke and McBain (2006)
	-75.3 ± 0.9	-78 ± 2	Cell-attached GABA application ^b	Tyzio et al. (2008)
STR- and STP/STO INs	-65-69	-61-66		
	-69.1 ± 1.0	-66.0 ± 1.0	Cell-attached GABA application ^b	Tyzio et al. (2008)
	-65.3 ± 1.0	-60.5 ± 0.7	Synaptic stimulation	Lamsa and Taira (2003)
SL-INs	-78	-75		
	-78.1 ± 3.7	-75.4 ± 2.5	Synaptic stimulation	Banke and McBain (2006)
CA1				
PC	-69	-66		
	-69 ± 4	-66.0 ± 0.5	Synaptic stimulation	Riecki et al. (2008)
	-67.8 ± 2.3	-63.2 ± 1.0	Synaptic stimulation	Sauer et al. (2012)

Abbreviations: GC granule cell, BC basket cell, PC pyramidal cell, STR stratum lucidum, STP stratum pyramidale, STO stratum oriens, SL stratum lucidum
^aRecorded at room temperature; ^bGABA receptor reversal potential depicted from cell-attached recordings of individual GABA channels

corresponding V_{rest} of -78 ± 2 mV (Table 3; Tyzio et al. 2008). Similarly, in CA1, some discrepancy persists about the nature of GABAergic inhibition. Perforated-patch recordings from CA1 PyCs indicated shunting or slightly hyperpolarizing inhibition (Table 3, Riecki et al. 2008). In contrast, unitary field recording with distinct IN types including BCs, AA, O-LM, and bistratified cells as the presynaptic neuron was always hyperpolarizing (Glickfeld et al. 2009; Sauer et al. 2012). Differences in the excitation state of the recorded cells (Lamsa and Taira 2003), modulation of Cl^- transporters (Woodin et al. 2003) or differences in membrane properties between neurons in different brain areas might explain the variability in the obtained E_{syn} values.

In summary, synaptic GABA_AR-mediated synaptic inhibition onto INs is largely shunting, independent of the nature of the recorded IN type or the hippocampal area. However, synaptic inhibition in PCs is diverse and varies from hyperpolarizing to shunting and even depolarizing inhibition.

GABA_BR-Mediated Inhibition in Hippocampal Circuits

Early electrophysiological and pharmacological studies demonstrated that, in addition to fast ionotropic GABA_ARs, slow-acting metabotropic GABA_BRs are also involved in the mediation of the effects of GABA in the hippocampus. In CA1 PyCs, extracellular stimulation in the *str. radiatum* elicits a biphasic IPSP consisting of a fast and a slow component (Newberry and Nicoll 1984; Dutar and Nicoll 1988b). While the fast component of the compound IPSP is blocked by the GABA_AR antagonist bicuculline, the slow component persists under bicuculline application (Newberry and Nicoll 1984; Dutar and Nicoll 1988b) and can be blocked by the GABA_BR antagonist CGP35348 (Fig. 2a; Solís and Nicoll 1992). Similarly, stimulation in dendritic layers elicits slow GABA_BR-mediated inhibitory responses in CA3 PyCs, dentate gyrus GCs, and various types of INs (Thompson and Gähwiler 1992; Otis et al. 1993; Khazipov et al. 1995; Mott et al. 1999; Booker et al. 2013, 2017b). Results of these studies, thus, indicate a widespread and abundant postsynaptic localization of GABA_BRs in the dendrites of PCs and INs (Sibbe and Kulik 2017; Kulik et al. 2017).

GABA_BRs are also expressed presynaptically where they modulate release of various neurotransmitters and neuromodulators (Sibbe and Kulik 2017; Kulik et al. 2017). Presynaptic receptors are commonly subdivided into autoreceptors and heteroreceptors (Bettler et al. 2004) depending on whether they control the release of GABA from inhibitory terminals (Booker et al. 2013, 2017a) in a feedback manner (Davies et al. 1991) or act at the axon terminals of other transmitter systems (e.g., glutamatergic axons; Vogt and Nicoll 1999; Kulik et al. 2002, 2003; Guetg et al. 2009; Oláh et al. 2009).

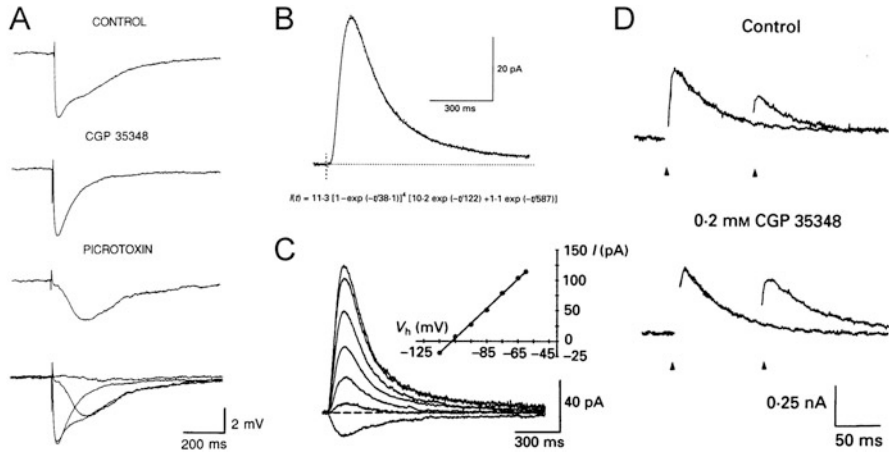


Fig. 2 GABA_BR-mediated effects in hippocampal neurons. **(a)** Pharmacological dissection of the monosynaptic IPSP reveals the fast GABA_A and the slow GABA_BR-mediated IPSP components in a CA1 PyC. **B,C** Kinetics **(b)** and reversal potential **(c)** of the GABA_BR-mediated slow IPSC in dentate gyrus GCs. **(d)** Activation of GABA_B autoreceptors contribute to depression of IPSCs in response to paired stimuli (top trace, arrow). CGP 35348, a GABA_B receptor antagonist relieves presynaptic inhibition and increases the amplitude of the second response (bottom trace, arrow). **(a)** adapted from Solís and Nicoll 1992; **b** and **c** adapted from Otis et al. 1993; **d** adapted from Davies and Collingridge 1993 with permission, © The Society for Neuroscience and The Physiological Society)

Structure and Signaling Through Metabotropic GABA_BRs

GABA_BRs belong to the family of seven transmembrane domain G protein-coupled receptors (GPCRs) (Kaupmann et al. 1997). Two different genes, encoding the GABA_{B1} – which occurs in alternatively spliced forms designated GABA_{B1a-n} – and the GABA_{B2}, subunits have so far been identified (Kaupmann et al. 1997; Isomoto et al. 1998; Pfaff et al. 1999; Schwarz et al. 2000; Wei et al. 2001; Lee et al. 2010). As regards GABA_{B1}, the GABA_{B1a} and GABA_{B1b} transcripts are the most abundant throughout the central nervous system (CNS), exhibiting differences in the extracellular NH₂-terminal domain (Kaupmann et al. 1997). Although there are indications that splice variants exist for GABA_{B2} (GABA_{B2a-c}) (Billinton et al. 2001), more recent results suggest that GABA_{B2b} and GABA_{B2c} transcripts may represent artifacts arising during cDNA synthesis and/or PCR amplification (Bettler et al. 2004).

For their surface localization, efficient coupling to the physiological effectors and formation of fully functional receptors, assembly of heterodimeric complexes made up of GABA_{B1} and GABA_{B2} subunit isoforms is required (Jones et al. 1998; White et al. 1998; Kaupmann et al. 1998a; Marshall et al. 1999; Kuner et al. 1999; Bettler

et al. 2004; Pin and Bettler 2016). The independently regulated GABA_{B(1a;2)} and GABA_{B(1b;2)} receptor subtypes differentially compartmentalize and fulfill distinct pre- vs. postsynaptic functions, respectively, in cortical PCs and INs (Pérez-Garci et al. 2006; Vigot et al. 2006; Shaban et al. 2006; Guetg et al. 2009). In the heterodimers, the GABA_{B1} protein contains the ligand-binding domain, whereas the GABA_{B2} subunit interacts with G proteins (Kaupmann et al. 1998a).

Recent biochemical and electrophysiological studies, prompted by the diversity in properties and characteristics of GABA_BR responses, provided compelling evidence that a further variety of molecularly and functionally distinct types of GABA_BRs exist (Schwenk et al. 2016; Bettler and Fakler 2017; Fritzius et al. 2017). The diversity of the native GABA_BRs originates from the co-assembly of the GABA_BR subunits with numerous types of auxiliary proteins (Gassmann and Bettler 2012; Schwenk et al. 2016). One of the most abundant and best studied constituents of the GABA_BR macromolecular complex is the K⁺ channels tetramerization domain-containing (KCTD) family of proteins (Schwenk et al. 2010; Bartoi et al. 2010; Metz et al. 2011; Turecek et al. 2014). Four KCTD proteins, designated KCTD8, KCTD12, KCTD12b, and KCTD16, associate with the GABA_{B2} subunit and determine the kinetics and pharmacology, including agonist potency and G protein signaling, as well as the desensitization of the receptor response in both dendritic and axonal compartments of the cells (Schwenk et al. 2010; Adelfinger et al. 2014; Rajalu et al. 2015; Booker et al. 2017b). Two recent elegant pharmacological studies provided direct evidence for the involvement of both KCTD12 and KCTD16 in determining phenotypes of behavioral activity, emotionality, as well as neuronal excitability (Cathomas et al. 2015, 2017). Furthermore, high-resolution functional proteomics more precisely identified the building blocks of GABA_BRs: the receptor core is assembled from GABA_{B1}, GABA_{B2}, KCTD proteins, and a distinct set of G protein subunits, whereas the periphery of the receptor's nanoenvironment is formed by transmembrane proteins (Schwenk et al. 2016). These peripheral constituents can operate as effectors (Schwenk et al. 2016); can be, via interaction with sushi domains, mediators of cellular processes that direct the trafficking of GABA_{B(1a;2)} receptors into the appropriate compartment of neurons (Tiao et al. 2008); or may represent linkers between GABA_BRs and cellular signaling processes (Sakaba and Neher 2003; Pettem et al. 2013).

As GPCRs, effects of GABA_BR complexes are mediated by second messenger cascades regulating the activity of adenylyl cyclase and phospholipase A₂, as well as effector channels such as G protein-coupled inwardly rectifying K⁺ (Kir3) channels or low and high-voltage-activated Ca²⁺ (Ca_v) channels (Marshall et al. 1999; Pérez-Garci et al. 2006; Gassmann and Bettler 2012; Sibbe and Kulik 2017; Kulik et al. 2017; Booker et al. 2018). Accordingly, application of pertussis toxin, an adenylyl transferase, which inactivates several types of G_i proteins, or GDPβ-S, a structural analog of GDP, which competes with GTP for the G protein-binding site, abolishes both pre- and postsynaptic effects of GABA_BRs in hippocampal PyCs (Andrade et al. 1986; Dutar and Nicoll 1988b; Thompson and Gähwiler 1992; Sodickson and Bean 1996).

Postsynaptic Slow Inhibition Mediated by GABA_BRs

Functional properties of postsynaptic GABA_BR-mediated responses are markedly different from those of fast GABA_AR-dependent signaling. First, GABA_B IPSCs have a much slower time course (Fig. 2b). Pharmacologically isolated slow IPSCs have a long onset latency (~12–20 ms, Otis et al. 1993; Table 4), reflecting the multiple steps leading up to the activation of the receptors and their G protein-mediated coupling to the effectors. Furthermore, GABA_B IPSCs have very slow rise and decay. In dentate gyrus GCs, the rise of the IPSC could be described by a fourth-order exponential with an activation time constant of ~45 ms and the decay by a biexponential function with time constants of ~110 and ~516 ms (Otis et al. 1993; Fig. 2b; Table 4). Similarly slow kinetics of GABA_B IPSCs have been reported in CA1 PyCs (Davies et al. 1990; Ling and Benardo 1994; Degro et al. 2015) and in various types of INs (Khazipov et al. 1995; Mott et al. 1999; Booker et al. 2013, 2017b; Table 4).

Second, ionic mechanisms of GABA_BR-mediated postsynaptic effects are also different from those of GABA_ARs. Slow IPSPs and baclofen-induced currents reverse close to the estimated equilibrium potential of K⁺ ions, in the range between –90 and –100 (Fig. 2c and Table 4), indicating that GABA_BRs activate a K⁺-selective conductance (Gähwiler and Brown 1985; Davies et al. 1990; Thompson and Gähwiler 1992; Ehrenguber et al. 1997; Booker et al. 2013; Degro et al. 2015). Furthermore, application of Ba²⁺, an inhibitor of inwardly rectifying K⁺ (Kir) channels, abolishes these effects (Gähwiler and Brown 1985; Thompson and Gähwiler 1992; Sodickson and Bean 1996). In fact, the channels mediating the GABA_B responses have been identified as the Kir3 channel subfamily (Lüscher et al. 1997; Kaupmann et al. 1998b). Kir3 channels comprise four subunits (Kir3.1-3-4; Dascal 1997) and form homotetrameric or heterotetrameric complexes (Krapivinsky et al. 1995; Inanobe et al. 1995; Kofuji et al. 1995; Spauschus et al. 1996; Slesinger et al. 1996; Liao et al. 1996; Wischmeyer et al. 1997). In the hippocampus, Kir3 channels are thought to be mainly composed of the Kir3.1 and Kir3.2 subunits (Lesage et al. 1995; Duprat et al. 1995; Leaney 2003). The Kir3.2 subunit is an essential part of the functional channel, determining its assembly and surface localization (Inanobe et al. 1999; Ma et al. 2002; Lujan et al. 2009), whereas Kir3.3 protein contains a lysosomal-targeting motif that reduces its surface expression and accumulation (Ma et al. 2002). In Kir3.2 knockout animals, expression of Kir3.1 is reduced, and slow inhibitory postsynaptic responses are abolished (Liao et al. 1996; Signorini et al. 1997; Lüscher et al. 1997). In good agreement with the proposed coupling of GABA_BRs and Kir3 channels, immunocytochemical investigations revealed robust colocalization of the two proteins in dendrites of CA PyCs and various types of INs (Kulik et al. 2006; Booker et al. 2013; Degro et al. 2015; Booker et al. 2017b).

In addition to regulating Kir3 channels, dendritic GABA_BRs have been shown to inhibit Kir2 channels (Rossi et al. 2006) and modulate Ca_v channels in cortical PCs and INs. Recent studies provided evidence that GABA_BRs can inhibit Ca_v1.2 (L-

Table 4 Properties of GABA_B receptor-dependent IPSCs

Cell type	Onset latency (ms)	Rise ^a (ms)	Decay ^b (ms)	Peak conductance (nS)	Reversal potential (mV)	Publication
DG GCs	12–20	$\tau = 45 \pm 1$	$\tau_1 = 110 \pm 7$	1.52 ± 0.16	-98 ± 2	Otis et al. (1993)
			$\tau_2 = 516 \pm 53$			
	27 ± 3	$T_{\text{peak}} = 162 \pm 15$	$\tau_1 = 133 \pm 11$	1.31 ± 0.23	-95 ± 2	Mott et al. (1999)
			$\tau_2 = 649 \pm 65$			
DG INs	53.5 ± 7.3	$T_{\text{rise}} = 86.8 \pm 7.0$	$T_{\text{decay}} = 428.1 \pm 89.6$	1.82 ± 0.18 ^c	-98.3 ± 5.8 ^c	Degro et al. (2015)
			$\tau = 261 \pm 28$			
BC/HICAP				1.25		
HIPP/TML				0.36		
CA1 PCs	29 ± 2	$T_{\text{rise}} = 110$	$T_{\text{IPSC}} = 723 \pm 135$	0.94 ± 0.28	-93 ± 2	Davies et al. (1990)
			62 ± 11			
			$\tau_2 = 247 \pm 32$			
	58.6 ± 4.6	$T_{\text{rise}} = 55.3 \pm 5.3$	$\tau = 200.5 \pm 37.7$	2.46 ± 0.37 ^c	-101 ± 5 ^c	Booker et al. (2013)
CA1 Ins						
CA1 str. rad. INs		$T_{\text{rise}} = 118 \pm 6$	$T_{\text{decay}} = 185 \pm 14$	0.79 ± 0.18	-94 ± 8	Khazipov et al. (1995)
CA1 PV BC	78.1 ± 10.7	$T_{\text{rise}} = 80.7 \pm 7.9$	$T_{\text{decay}} = 152.9 \pm 24.3$	3.56 ± 0.61 ^c	-95 ± 12 ^c	Booker et al. (2013)
CA1 PV Bistratified				0.38 ± 0.24 ^c		Booker et al. (2013)
CA1 CCK BC	56.3 ± 3.0	$T_{\text{rise}} = 73.0 \pm 2.5$	$T_{\text{decay}} = 141.4 \pm 5.2$	2.31 ± 0.14 ^c		Booker et al. (2017b)
CA1 CCK SCA				0.80 ± 0.04 ^c		Booker et al. (2017b)
CA1 CCK PPA				0.88 ± 0.20 ^c		Booker et al. (2017b)

Abbreviations: BC basket cell, HICAP hilar commissural-associational pathway-associated cell, HIPP hilar perforant pathway-related cell, TML total molecular layer cell, SCA Schaffer-collateral-associated cells, PPA perforant path-associated cells

^aValues indicate either the time constant (τ) of fitted fourth-order exponential function, peak latency (T_{peak}), or rise time (T_{rise}) measured from onset to peak

^bValues indicate the time constants of mono- (τ) or biexponential (τ_1, τ_2) functions fitted to the decay, the full duration (T_{IPSC}) or the decay half-time (T_{decay})

^cBaclofen-induced whole-cell currents; reversal potential determined using voltage-ramps from -20 to -120 mV (1 s duration); in CCK INs a reversal potential of -95 mV was assumed

type), $Ca_v2.1$ (P/Q-type), $Ca_v2.2$ (N-type), and $Ca_v2.3$ (R-type) channel-mediated dendritic spikes in prefrontal cortical neurons (Chalifoux and Carter 2011) and in layers 2/3 and 5 somatosensory neocortical PyCs (Pérez-Garci et al. 2006, 2013; Larkum et al. 2007). GABA_BRs have also been shown to inhibit $Ca_v1.2$ channels in dendrites of hippocampal somatostatin-expressing INs (SOM-INs) and abolish thereby the induction of long-term potentiation (LTP) at their excitatory input synapses (Booker et al. 2018).

Presynaptic Inhibition of Synaptic Transmission by GABA_BRs

Presynaptic GABA_BRs play an important role in regulating synaptic transmission at both excitatory and inhibitory synapses. At excitatory synapses, their activation results in depression of glutamatergic synaptic responses (Lei and McBain 2003). Evidence for presynaptic effects of GABA has been obtained at various hippocampal afferent pathways including the hippocampal CA3-CA1 and MF-CA3 PyC synapses (Vogt and Nicoll 1999; Vigot et al. 2006; Guetg et al. 2009). At these synapses, it has been shown that synaptically released GABA suppresses Schaffer collateral and MF responses through GABA_BRs, predominantly via GABA_{B(1a;2)} receptors (Vigot et al. 2006; Guetg et al. 2009). Thus, GABA spilling over from local inhibitory synapses can regulate glutamatergic transmission by heterosynaptic inhibition at various cortical synapses (Vogt and Nicoll 1999; Oláh et al. 2009; Urban-Ciecko et al. 2015). As many DI cells have axons co-aligned with afferent pathways (Gulyás et al. 1993; Han et al. 1993; Vida et al. 1998; Vida and Frotscher 2000; see chapter “[Morphology of Hippocampal Neurons](#)”), this mechanism enables INs to provide input-specific presynaptic control through heterosynaptic inhibition to the main afferent systems to the hippocampal areas (Sohal and Hasselmo 1998).

Presynaptic action of GABA_BRs is primarily dependent on G protein-mediated inhibition of the Ca^{2+} conductance (Bettler et al. 2004). Paired recordings from calyx of Held terminals and postsynaptic neurons in the medial nucleus of the trapezoid body provided direct evidence that activation of the receptors by baclofen has no effect on presynaptic K^+ conductances but inhibits Ca^{2+} currents in these terminals (Takahashi et al. 1998). It has been further demonstrated that the presynaptic effect of baclofen is also blocked by GDP β -S (Takahashi et al. 1998). In the hippocampus, direct patch-clamp recordings from presynaptic elements cannot be routinely performed, with the exception of the large MF terminals on CA3 PyCs (e.g., Geiger and Jonas 2000). Nevertheless, overwhelming evidences suggest that the main mechanisms underlying presynaptic GABA_BR responses at hippocampal synapses also involve Ca_v channels (Bettler et al. 2004; Ulrich and Bettler 2007; Laviv et al. 2011; Vertkin et al. 2015). Presynaptic depression of EPSPs by baclofen is unaffected by Ba^{2+} in cultured hippocampal PyCs (Thompson and Gähwiler 1992), and remains also unchanged in slices from Kir3.2 (GIRK2) knockout mice (Lüscher et al. 1997). In contrast, Ca^{2+} currents evoked in cultured PyCs and INs are highly sensitive to baclofen (Scholz and Miller 1991). Most

compellingly, the inhibitory effects of baclofen on fast presynaptic Ca^{2+} transients and field EPSPs show similar time course in CA1 PyCs (Wu and Saggau 1995). Thus, presynaptic inhibition of excitatory transmission by GABA_B Rs depends on reduction in Ca^{2+} conductance rather than activation of K^+ currents in the hippocampus (Gassmann and Bettler 2012). However, the involved Ca^{2+} channel types seem to differ at the various synapses. In CA1 PyCs GABA_B R-mediated presynaptic inhibition is occluded by the application of ω -conotoxin, a selective $\text{Ca}_v2.2$ Ca^{2+} channel blocker, but not affected by ω -agatoxin, a blocker of $\text{Ca}_v2.1$ channels (Wu and Saggau 1995). In contrast, in CA3 *str. radiatum* INs ω -conotoxin and ω -agatoxin occlude presynaptic inhibitory effects of baclofen on miniature EPSCs to an equal degree (Lei and McBain 2003). However, evidence exists that the control of transmitter release by GABA_B R not only acts through Ca^{2+} channels reducing presynaptic release itself but may also lead to altered short-term plasticity independent of the change in release probability (Lei and McBain 2003; Booker et al. 2017a), pointing to more direct interactions with the release machinery.

At hippocampal GABAergic synapses, activation of presynaptic GABA_B Rs, both $\text{GABA}_{B(1a;2)}$ and $\text{GABA}_{B(1b;2)}$ receptor types (Vigot et al. 2006), results in reduced inhibitory transmission (Doze et al. 1995; Poncer et al. 2000; Booker et al. 2017a). Consequently, repetitive stimulation leads to the attenuation of IPSCs (“autoinhibition,” Davies et al. 1991; Mott and Lewis 1991; Fig. 2d). This dynamic modulation of inhibitory transmission has an important function in regulating the induction of LTP in the hippocampus (Davies et al. 1991; Mott and Lewis 1991). The molecular mechanism of GABA_B R-dependent presynaptic inhibition in GABAergic terminals has extensively been investigated. In an early study, effects of baclofen on unitary IPSPs in synaptically coupled pairs of cultured hippocampal neurons were not affected by pre-treatment with pertussis toxin (Harrison 1990). Others have reported that pertussis toxin abolished the baclofen-induced depression of IPSPs in cultured CA3 PyCs (Thompson and Gähwiler 1992). Similarly, findings about the ionic mechanism of presynaptic GABA_B Rs have remained somewhat controversial. Thompson and Gähwiler (1992) have shown that extracellular Ba^{2+} reduces presynaptic depression of IPSPs by baclofen in cultured CA3 PyCs, suggesting a contribution of K^+ channels, plausibly of the Kir3 type. Furthermore, baclofen decreases the frequency of both spontaneous IPSCs and action potential- and Ca^{2+} -independent miniature IPSCs recorded in the presence of tetrodotoxin (Lei and McBain 2003). Increased frequency of miniature IPSCs by elevated levels of extracellular KCl is blocked by Cd^{2+} , and the additional application of baclofen leads to a further reduction in the IPSC frequency (Lei and McBain 2003). Thus, in GABAergic terminals the coupling of presynaptic GABA_B Rs may, at least partially, utilize pertussis toxin-insensitive G proteins and activate K^+ channels or directly affect the synaptic release machinery in addition to the inhibition of Ca_v channels. Furthermore, there is also evidence that the modulation of K^+ and Ca_v channels is not the only mechanism by which GABA can regulate transmitter release: whole-cell recordings from CA1 PyCs demonstrated that inhibition of GABA release by GABA_B Rs is reduced by an activator of protein kinase C (PKC) (Jarolimek and Misgeld 1997).

Cellular and Subcellular Localization of Postsynaptic GABA_BRs

Consistent with the physiological and pharmacological data, *in situ* hybridization (Kaupmann et al. 1998a; Bischoff et al. 1999) and autoradiography (Bowery et al. 1987; Chu et al. 1990) confirmed the abundant expression of GABA_BR subunits in hippocampal PCs and INs. Subsequent immunocytochemical studies (Fritschy et al. 1999; Sloviter et al. 1999; Margeta-Mitrovic et al. 1999; Kulik et al. 2002, 2003) further revealed the cellular and subcellular distribution and localization of the GABA_BR subunits. At the light microscopic level, the immunostaining for the two subunits, GABA_{B1} and GABA_{B2}, showed very similar patterns of distribution in the hippocampus (Fig. 3a, b). In the CA areas and the dentate gyrus, immunoreactivity was most intense over the dendritic layers. The *str. lacunosum-moleculare* of CA3 showed the strongest labeling for the proteins, whereas in CA1 the immunoreactivity for the receptor subunits was generally weak to moderate. In the dentate gyrus, the immunolabeling was weak in the hilus and moderate in the molecular layer (Fritschy et al. 1999; Margeta-Mitrovic et al. 1999; Kulik et al. 2003).

At the subcellular level, the immunolabeling for both GABA_{B1} and GABA_{B2} was observed in postsynaptic and, to a lesser extent, presynaptic compartments of PCs (Fig. 3c–e). Postsynaptically, the majority of the receptor subunits were localized to the extrasynaptic plasma membrane of dendritic spines and shafts of PyCs and dentate GCs (Kulik et al. 2003). Quantitative analysis further revealed an enrichment of GABA_BRs around excitatory synapses on dendritic spines, and an even distribution on dendritic shafts of PyCs contacted by GABAergic axon terminals (Fig. 3f, g; Kulik et al. 2003). Interestingly, the effector Kir3 channels displayed a very similar cellular and subcellular distribution (Koyrakh et al. 2005; Kulik et al. 2006). Moreover, GABA_BRs and Kir3 channels were found to be co-clustered around excitatory synapses on dendritic spines of PyCs (Fig. 3g; Kulik et al. 2006) indicating the functional association of these two proteins in this subcellular compartment. The enrichment of the GABA_BR-Kir3 channel complexes in spines implies their intimate involvement in the control of synaptic integration and plasticity. Indeed, GABA_BR-mediated inhibition has been shown to act as a break on NMDA receptor-mediated responses and thereby reduced synaptic plasticity in PyCs (Otmakhova and Lisman 2004; Malenka and Bear 2004). Conversely, activation of NMDA receptors and Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), as well as rise in postsynaptic Ca²⁺ results in LTP of the GABA_BR-Kir3 channel-mediated slow IPSPs, which parallel the time course of LTP of excitatory transmission (Huang et al. 2005). The functional significance of this IPSC potentiation is to sharpen the coincidence detection of synchronous excitatory inputs (Huang et al. 2005), a hallmark for learning and memory. Moreover, activation of NMDA receptors along with CaMKII can regulate the surface expression and function of GABA_BRs: prolonged activation of glutamate receptors results in endocytosis and subsequent degradation of GABA_BRs (Terunuma et al. 2010; Guetg et al. 2010).

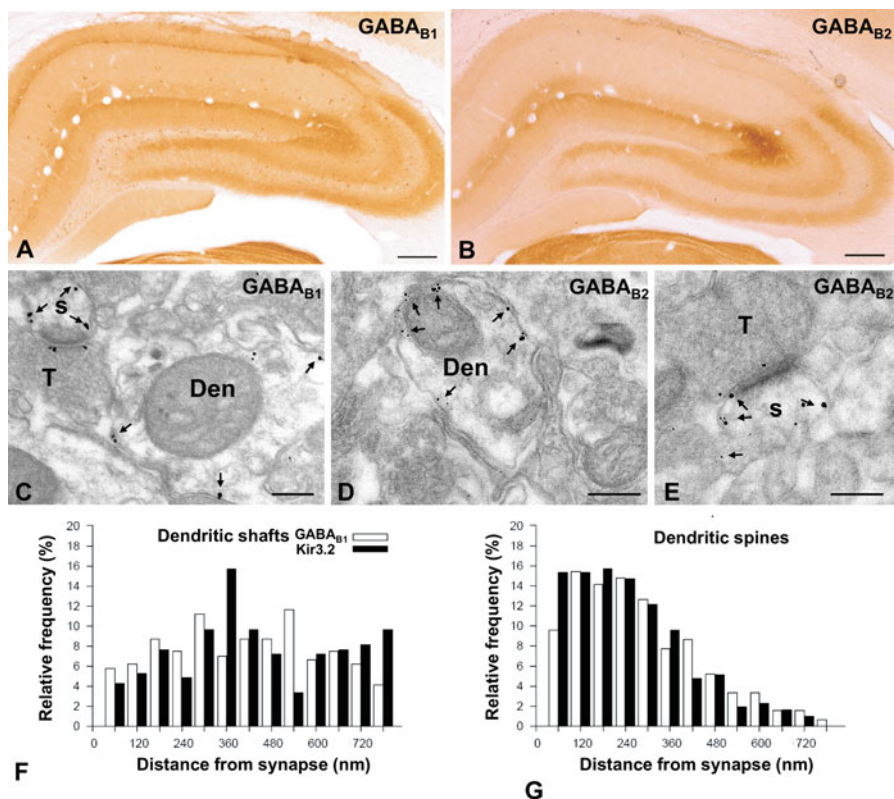


Fig. 3 Cellular and subcellular distribution of GABA_BRs in the hippocampus. (a and b) Light micrographs show the distribution of immunoreactivity for GABA_{B1} and GABA_{B2} in the hippocampus. Strong labeling for the subunits was observed in dendritic layers of CA areas and dentate gyrus. Strong immunoreactivity for GABA_{B1}, but not for GABA_{B2}, was detected in somata of CA1 pyramidal cells and INs. (c–e), Electron micrographs show pre-embedding immunogold labeling for the receptor subunits in pre- and postsynaptic compartments of pyramidal cells. Immunogold particles for GABA_{B1} and GABA_{B2} were detected on the synaptic membranes (arrowheads in c and e) of the axon terminals (T), as well as on the extrasynaptic membranes (arrows in c–e) of dendritic spines (s) and dendritic shafts (Den) of pyramidal cells. (f and g) Histograms illustrate the distribution of immunoparticles for GABA_{B1} and Kir3.2 relative to symmetrical and asymmetrical synapses on dendrites of CA1 pyramidal cells. Note the enrichment of both molecules in the vicinity of asymmetrical, putative glutamatergic synapses on dendritic spines (g), but not around symmetrical, putative inhibitory synapses on shafts (f). Scale bars: a and b, 200 μm; c–e, 0.2 μm (a adapted from Kulik et al. 2003; f and g adapted from Kulik et al. 2006 with permission, © Society for Neuroscience)

Presynaptically, the immunolabeling for GABA_BRs is substantially weaker. Nevertheless, immunoreactivity has been consistently found in glutamatergic axon terminals forming asymmetrical synaptic contacts (Kulik et al. 2003). The labeling intensity was higher in these boutons than in putative inhibitory terminals making symmetrical synapses (see below). The receptor subunits were mainly detected

at the extrasynaptic plasma membrane and occasionally over the presynaptic membrane specialization (Fig. 3c, e; Kulik et al. 2003). Recent results further showed that, while postsynaptic receptors are mainly composed of the GABA_{B1b} and GABA_{B2} subunits (GABA_{B(1b;2)} receptors), terminals of excitatory afferents, including the Schaffer collaterals and the MFs, preferentially contain receptors made up of GABA_{B1a} and GABA_{B2} subunits (GABA_{B(1a;2)} receptors, Vigot et al. 2006; Guetg et al. 2009). Interestingly, receptors with the latter subunit composition have a higher sensitivity for baclofen and GABA and can mediate heterosynaptic inhibition of glutamatergic transmission by synaptically released GABA (Guetg et al. 2009).

Functional GABA_BRs in Hippocampal Inhibitory Interneurons

In addition to labeling in PCs, immunoreactivity for GABA_BR subunits was also found in various subpopulations of INs. At the light microscopic level, strong immunostaining for the GABA_{B1} subunit, but not for the GABA_{B2} subunit, is present in cell bodies of a subset of GABAergic INs scattered throughout the hippocampus (Fritschy et al. 1999; Margeta-Mitrovic et al. 1999; Sloviter et al. 1999; Kulik et al. 2003). Electron microscopic investigation demonstrated that the strong somatic immunoreactivity for GABA_{B1} can be ascribed to the abundance of the protein in the endoplasmic reticulum (Kulik et al. 2003), conceivably reflecting a reserve pool of the receptor subunit. Fluorescence colocalization studies showed that INs with high somatic GABA_{B1} include PV-, CCK-, SOM-, neuropeptide Y-, calbindin-, and calretinin-containing cells (Sloviter et al. 1999; Booker et al. 2013, 2017b). Ultrastructural analysis further demonstrated that immunoreactivity for GABA_BRs is present postsynaptically along the extrasynaptic plasma membrane of dendritic shafts of NGFCs, PV-, CCK-, and SOM-expressing cells (Fig. 4a, b, f, g; Price et al. 2005; Booker et al. 2013, 2017b, 2018). Postsynaptic GABA_BRs were found to activate Kir3 channels in PV- and CCK-expressing BCs producing substantial slow IPSCs (Fig. 4c, d, h; Booker et al. 2013, 2017b), consistent with the expression of both the receptor and Kir3 channels on their dendritic membrane surface. Interestingly, in DI PV- and CCK-positive INs slow GABA_BR IPSCs were consistently smaller than in BCs suggesting IN type-specific expression of the functional receptors (Fig. 4e, h, i). Indeed, on archetypal dendrite-inhibiting SOM-INs postsynaptic GABA_BRs failed to produce substantial inhibitory currents, despite the presence of immunolabeling for both the channel and the receptor on the dendrites of these INs. Instead, in SOM-INs GABA_BR activation selectively inhibited Ca_v1.2 channels, leading to reduced Ca²⁺ influx and loss of LTP at excitatory synapses onto these INs (Booker et al. 2018).

Presynaptic GABA_BRs were also observed in GABAergic axon terminals, albeit at lower levels than in excitatory boutons (Kulik et al. 2003). Similar to glutamatergic terminals, the labeling was mainly found on the extrasynaptic and, to a lower degree, on synaptic membrane segments of inhibitory boutons. IN type specific data is scarce, however, in two recent studies PV- and CCK-positive

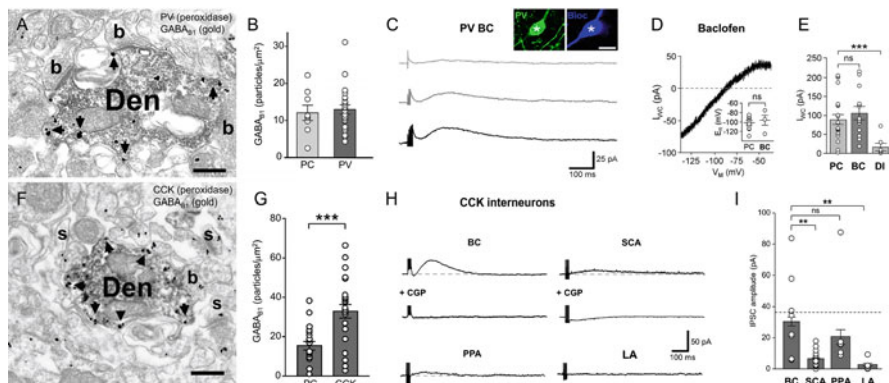


Fig. 4 Postsynaptic dendritic localization and effects of GABA_BR in hippocampal PV- and CCK-expressing INs. (a and f) Electron micrographs showing immunoreactivity for GABA_{B1} (immunoparticles, arrows) in dendritic shafts (Den) of PV- (a, peroxidase reaction end product) and CCK-positive INs (f, peroxidase) contacted by presynaptic boutons (b) in the CA1 str. radiatum. (b and g), Summary bar charts of the surface density of immunoparticles in dendrites of principal cells (PC), PV- (b) and CCK-positive INs (g). (c) Pharmacologically isolated slow GABA_BR IPSCs in a PV BC evoked by a single stimulus (top trace) or trains of 3 (middle) and 5 stimuli (bottom) elicited via an extracellular electrode. Inset shows the PV immunolabeling (left, green pseudocolor) in the biocytin-filled cell body (right, in blue). (d) Inwardly rectifying voltage dependence of the baclofen-induced current (I_{WC}) in a PV BC. Inset, summary of the reversal potential (E_R) of the baclofen-induced currents for PCs and BCs. (e) Summary chart of the baclofen-induced I_{WC} measured in PCs, PV-positive BCs and dendritic inhibitory (DI) INs. (h) Slow GABA_BR/Kir3-mediated IPSC in CCK-expressing INs elicited by 200 Hz train of 5 stimuli applied via an extracellular electrode. Slow IPSCs were recorded from a BC and a Schaffer collateral-associated cell (SCA), a perforant path-associated cell (PPA) and a lacunosum projecting cell (LA). The selective GABA_BR antagonist CGP fully blocked the IPSCs in BC and SCA cells (bottom traces). (i) Summary bar chart of the GABA_BR-mediated IPSC amplitudes recorded from CCK IN types. Bar charts show mean \pm SEM overlain by data from individual cells (open circles). Note that the mean IPSC in both PV and CCK DI cells was significantly smaller than in BCs. Scale bars: 0.2 μ m (a–e from Booker et al. 2013, f–j from Booker et al. 2017b. Reproduced with permission, © Society for Neuroscience and Wiley-Blackwell)

putative BC terminals in the *str. pyramidale* of the CA1 area were investigated comparatively (Booker et al. 2013, 2017a). Results obtained from quantitative SDS-digested freeze-fracture replica (SDS-FRL) immunoelectron microscopic analysis demonstrated a differential expression in these two bouton populations, while GABA_BRs were present at high densities on virtually all CB1-positive putative CCK terminals (Fig. 5a, b, e, f), they showed markedly lower densities and were expressed by only 40% of M2-positive putative PV boutons (Fig. 5c–f; Booker et al. 2017a). This expression pattern was in good agreement with the differential strength of presynaptic inhibition at these synapses: GABA release was dramatically (80–90%) inhibited by the receptor activation at CCK BC synapses, whereas it was reduced only moderately (\sim 50%) at PV BC synapses (Fig. 5g–i).

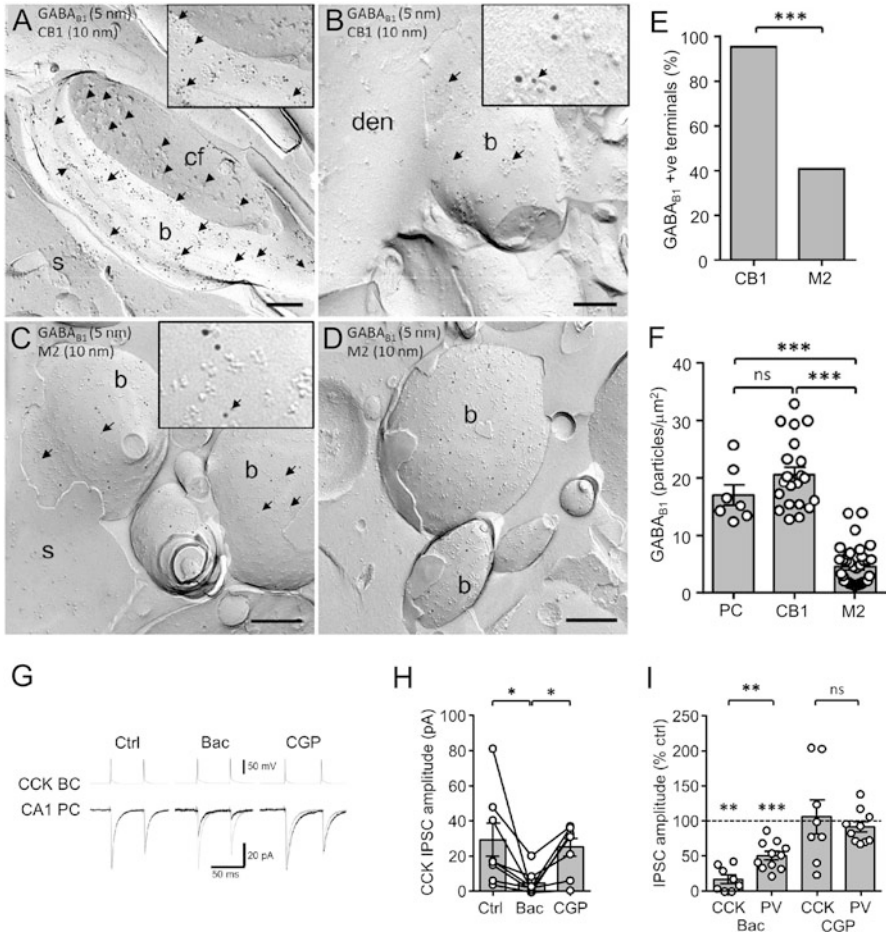


Fig. 5 Presynaptic axonal localization and effects of GABA_BRs in hippocampal CCK- and PV-positive INs. (**a–d**) Electron micrographs of freeze-fracture replicas showing the surface distribution of GABA_{B1} (5 nm particles, arrows) in CB1-positive (10 nm particles) putative CCK (**a** and **b**) and M2-positive (10 nm particles) putative PV boutons (**b**; **c** and **d**). (**e**) Summary bar chart of the proportion of GABA_{B1} on double-labeled CB1 receptor – or M2 receptor – containing the axon terminals. (**f**) Quantification of the density of immunoparticles for GABA_{B1} on CB1 receptor- and M2 receptor-positive axon terminals in comparison to PC dendrites. Statistics shown: *** $P < 0.0001$, Fisher’s exact test and 1-way ANOVA with multiple comparisons. (**g**) Action potentials elicited in the CCK BC (upper traces) evoked unitary IPSCs in the PC (lower traces) under control conditions (Ctrl, left panel), during bath application of the GABA_BR agonist baclofen (10 μM, middle) and the antagonist CGP (10 μM, right). (**h**) Summary chart of the IPSC amplitudes under control conditions, during baclofen and CGP application. (**i**) Summary bar chart of the normalized IPSC amplitudes for a comparison of baclofen-induced inhibition at CCK and PV BC synapses; recovery in CGP is shown for both types on the right. Statistics: ns $P \geq 0.05$, * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$. Abbreviations: cf, cross-fractured; S, soma; den, dendritic shaft. Scale bars, 0.2 μm. (Reproduced from Booker et al. 2017a, © The Authors)

Activation of GABA_BRs by Spillover of GABA from Inhibitory Synapses

Conditions for the activation of GABA_BRs differ dramatically from those of GABA_ARs (Farrant and Nusser 2005; Kulik et al. 2017). Whereas GABA_AR-mediated responses are readily observed at low-stimulus intensities and in paired recordings of synaptically coupled neurons, strong and/or repetitive stimulation is required to elicit GABA_BR-mediated postsynaptic effects (Newberry and Nicoll 1985; Isaacson et al. 1993), indicating that recruitment of a number of GABAergic neurons and the release of larger amount of GABA is necessary for the activation of the receptors. It was estimated that the simultaneous recruitment of ~2–20 INs is required to induce slow GABA_B IPSPs (Scanziani 2000).

These differences between the two receptor types appear to contradict the fact that the affinity of GABA_BRs for GABA is ~16-fold higher than that of GABA_ARs. Sodickson and Bean (1996) showed that the EC₅₀ for the activation of GABA_BR-mediated potassium conductance by GABA is much lower (1.6 mM) than for the activation of GABA_AR-mediated chloride conductance (25 mM). However, this apparent discrepancy can be explained by the differential localization of the two types: while GABA_ARs are clustered primarily in synapses opposite to the GABA release sites (Nusser and Somogyi 1997; Farrant and Nusser 2005), GABA_BRs are preferentially localized to the extrasynaptic membrane at some distance from GABAergic synapses (Kulik et al. 2003; Fig. 6). Thus, for the

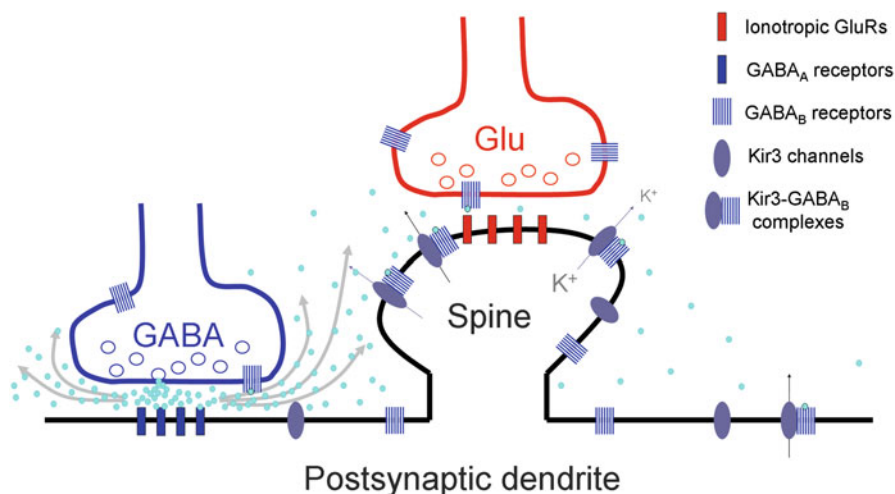


Fig. 6 Activation of the pre- and postsynaptic GABA_BRs by GABA spillover from inhibitory terminals. Abbreviations: GABA – GABAergic terminal, Glu – glutamatergic terminals, blue circles represent GABA molecules released from the inhibitory terminal. (Modified from Kulik et al. 2003 with permission, © Society for Neuroscience)

activation of GABA_BRs GABA needs to flow out from the inhibitory synapses and diffuses through the extracellular space before it can reach the receptors (“spillover hypothesis,” Isaacson et al. 1993). In order to achieve sufficiently high concentration of GABA at the location of the receptors, release from larger number of GABAergic terminals is required in a given volume (Newberry and Nicoll 1985; Dutar and Nicoll 1988a; Otis et al. 1993; Brown et al. 2007). Recent studies have, however, provided evidence that single NGFCs can produce activation of GABA_BRs in hippocampal and neocortical PCs (Tamás et al. 2003; Price et al. 2005, 2008; Oláh et al. 2009). A plausible explanation for this observation is that the highly dense focal axonal arbor of NGFCs enables this IN type to produce substantial volume transmission and evoke “unitary” GABA_BR-mediated responses in neighboring PyCs and other INs. Indeed, another study provides further evidence that GABA can spillover from synapses of NGFCs and activate extrasynaptic GABA_ARs and plausibly also GABA_BRs (Szabadics et al. 2007). However, in the presence of GABA uptake blockers, other IN types can also elicit GABA_BR-mediated currents in PCs and INs (Scanziani 2000; Booker et al. 2013), indicating that under physiological conditions efficient uptake mechanisms control activation of metabotropic GABA receptors in cortical networks.

In summary, under physiological conditions, GABA_BR-mediated responses are evoked upon concerted high activity of GABAergic INs. Such synchronous activity of large sets of INs occurs during network oscillations (see chapter “Cell Type-Specific Activity During Hippocampal Network Oscillations In Vitro”) and can, indeed, lead to the activation of GABA_BRs (Scanziani 2000). Conversely, GABA_BR-mediated effects can dynamically influence the frequency of the oscillations (Scanziani 2000; Booker et al. 2013). Thus, GABA_BRs can serve an important regulatory mechanism during rhythmic oscillatory and other population patterns in vivo. Such a role was further substantiated in recent set of experiments using in vitro models of cortical Up and Down state population activity: in these models activation of GABA_BRs promoted the termination of Up states recorded in the entorhinal cortex (Mann et al. 2009). This function of the receptors was contrasted by the role of GABA_AR-mediated inhibition, which was necessary for balancing persistent Up state activity (Mann et al. 2009). Interestingly, both pre- and postsynaptic GABA_BRs were involved in the termination of Up states, but in a differential manner: while presynaptic receptors containing the GABA_{B1a} subunit contributed to spontaneous ending of Up states (Craig et al. 2013), postsynaptic GABA_BRs containing the GABA_{B1b} subunit were found to be essential for afferent input-dependent active termination of Up states (Craig et al. 2013).

Future Perspectives

Although our understanding of the functional and dynamic properties of synaptic ionotropic GABA_AR- and the extrasynaptic, predominantly dendritic metabotropic GABA_BR-mediated signaling and the underlying mechanisms increased substan-

tially, several fundamental questions remained unanswered. What are the functional and dynamic characteristics of dendritically located GABAergic synapses? How does dendritic inhibition influence local integration of excitatory afferent inputs and thereby the input-output relation of target cells? How does dendritic inhibition contribute to neuronal network function such as information processing and network synchronization? Which other IN types express GABA_BRs and how do they contribute to signaling at the level of the individual neurons and the network? What are the additional constituents of the pre- and postsynaptic GABA_BR nanoenvironment? How dynamic is the functional and structural interaction of GABA_BRs with auxiliary proteins, neurotransmitter receptors, and effector ion channels?

Answering these questions is challenging and requires new experimental strategies and concepts. First, paired whole-cell patch-clamp recordings from synaptically connected INs in combination with light and electron microscopic analyses are required to determine synaptic properties, identity of recorded IN types, as well as the number and location of inhibitory synapses. Second, voltage-sensitive dye imaging in combination with whole-cell recordings are needed to examine dendritic integration of inhibitory and excitatory inputs. Third, *in vivo* whole-cell recordings from IN types together with biochemical and high-resolution quantitative immunoelectron microscopy would be useful to examine the kinetic and dynamic characteristics of synaptic inputs and receptor-associated network in dependence on the activity state of cortical circuits. Finally, a combined experimental and computational approach based on optogenetic analysis of synaptic and intrinsic physiological properties would be important to model integrative properties of the various IN types and to develop complex networks in order to identify the functional contribution of individual cell types and their synapses to network activity and information processing and network synchronization.

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