# *Interneuron Diversity series*: Fast in, fast out – temporal and spatial signal processing in hippocampal interneurons

**Peter Jonas[1], Josef Bischofberger[1], Desdemona Fricker[2] and Richard Miles[2]**

[1]Physiologisches Institut der Universität Freiburg, Hermann-Herder-Strasse 7, D-79104 Freiburg, Germany
[2]INSERM EMI0224, CHU Pitié-Salpêtrière, University Paris VI, 105 Boulevard de l'Hôpital, Paris 75013, France

**The operation of neuronal networks crucially depends on a fast time course of signaling in inhibitory interneurons. Synapses that excite interneurons generate fast currents, owing to the expression of glutamate receptors of specific subunit composition. Interneurons generate brief action potentials in response to transient synaptic activation and discharge repetitively at very high frequencies during sustained stimulation. The ability to generate short-duration action potentials at high frequencies depends on the expression of specific voltage-gated $K^+$ channels. Factors facilitating fast action potential initiation following synaptic excitation include depolarized interneuron resting potential, subthreshold conductances and active dendrites. Finally, GABA release at interneuron output synapses is rapid and highly synchronized, leading to a faster inhibition in postsynaptic interneurons than in principal cells. Thus, the expression of distinct transmitter receptors and voltage-gated ion channels ensures that interneurons operate with high speed and temporal precision.**

Interneurons play a key role in the operation of neuronal networks. Inhibitory cells control both the number of active pyramidal cells and their firing frequency by feedforward and feedback inhibition [1,2]. Interneurons also control the timing of principal cell discharge [1–3] and are thought to play a pivotal role in the generation of network oscillations [4–6]. In neuronal networks *in vivo* under a variety of behavioral conditions, interneurons generate action potentials precisely time-locked to the cycles of theta-, gamma- and high-frequency oscillations [7–11]. This suggests that interneurons could be involved in the generation and distribution of rhythmic activity in neuronal networks. Many of these functions of interneurons crucially depend on the fast and temporally precise conversion of an excitatory synaptic input into an inhibitory synaptic output. The complete sequence of interneuron activation, from synaptic excitation via dendritic integration to action potential initiation and GABA release, can occur within 1–2 ms [12–14]. This review examines, step by step, the molecular and cellular basis of this remarkably fast signal flow. For the purpose of illustration, it will focus on the hippocampus, a brain region with a well-defined anatomical layout. Although inhibitory cells are known to be highly diverse [15,16], this article will concentrate on interneuron subtypes that are well characterized, such as parvalbumin-positive basket cells (which form perisomatic contacts) and somatostatin-positive oriens alveus interneurons (which establish dendritic synapses on their target cells) [17,18].

## Fast glutamate-mediated excitation of interneurons

The first step is the excitation of GABAergic interneurons at glutamatergic synapses (Figure 1). As at other excitatory synapses, glutamate preferentially activates AMPA-type glutamate receptors. However, at excitatory synapses on interneurons, the AMPA-receptor-mediated excitatory postsynaptic current (EPSC) rises and decays rapidly [14,19,20] (Figure 1c). AMPA-receptor-mediated EPSCs at mossy fiber–basket cell synapses of the dentate gyrus, at mossy fiber–stratum lucidum interneuron synapses in the CA3 region, and at synapses on cerebellar interneurons have decay time constants of ~1.5 ms at 22°C and ~0.5 ms at 34°C [14,19,20] (Figure 1c). These fast kinetics depend primarily on the type of postsynaptic neuron, because AMPA-receptor-mediated EPSCs at mossy fiber synapses on interneurons are three times faster than those at mossy fiber synapses on CA3 pyramidal cells [21]. In addition, the type of presynaptic neuron might be important because AMPA-receptor-mediated EPSCs are significantly faster at mossy fiber synapses than at CA3 pyramidal cell collateral synapses on stratum lucidum interneurons (decay time constants of ~1.5 ms versus ~2.5 ms at 22°C) [20] (for characterization of stratum lucidum interneuron morphology, see Ref. [22]). High synchrony of quantal release, rapid clearance of transmitter at spine-free dendrites and fast gating of postsynaptic AMPA receptors help to generate rapid EPSCs at principal neuron–interneuron synapses [19]. In another review of this series, Lawrence and McBain [23] summarized how the gating properties of postsynaptic

*Corresponding author:* Peter Jonas (peter.jonas@physiologie.uni-freiburg.de).

 0166-2236/$ - see front matter  doi:10.1016/j.tins.2003.10.010

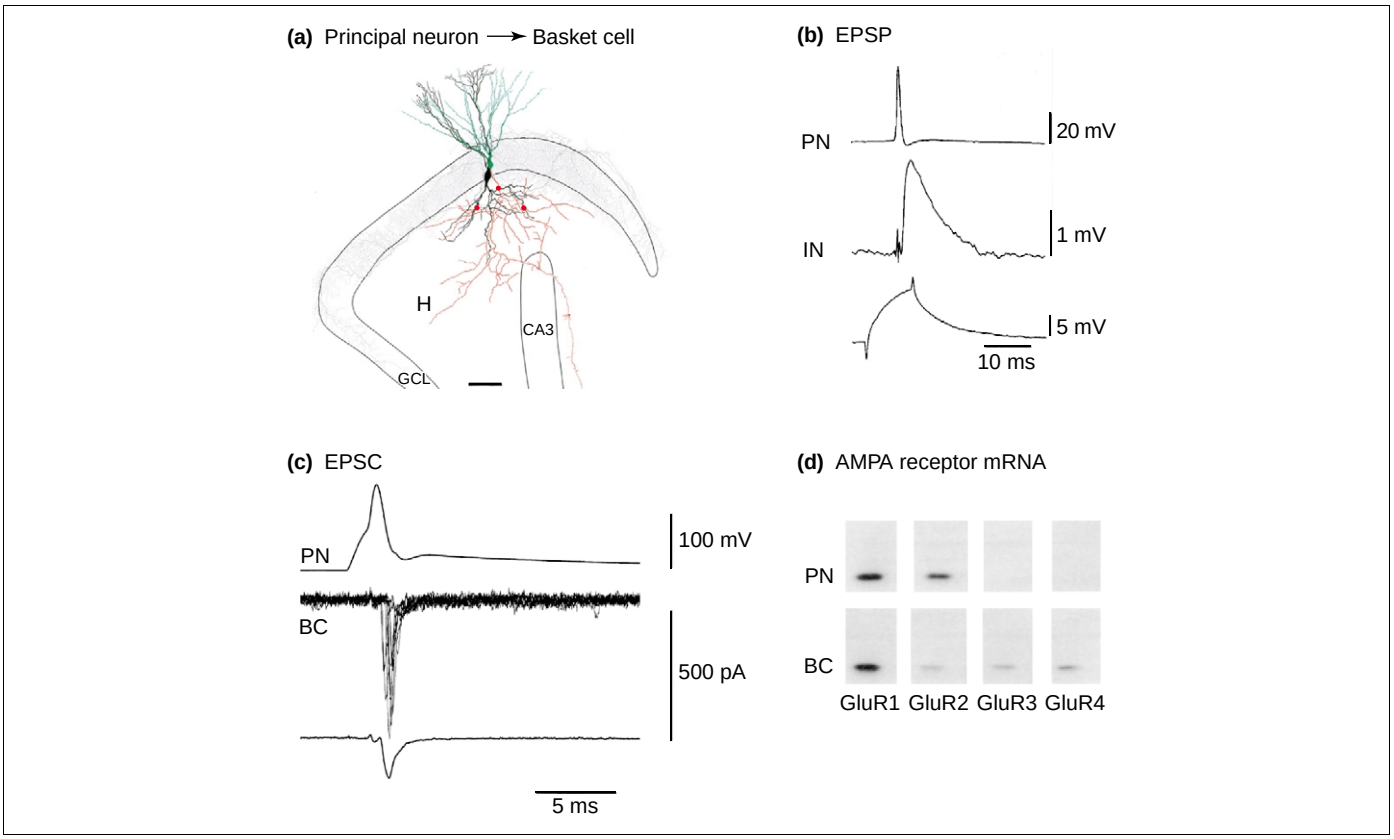


**Figure 1**. Fast AMPA-receptor-mediated excitation of hippocampal interneurons. **(a)** Morphological reconstruction of a reciprocally coupled granule cell (soma and dendrites, green; axon, red) and basket cell (soma and dendrites, black; axon, gray) pair in the dentate gyrus, with three putative excitatory synaptic contacts (red dots). Scale bar, 100 μm. Abbreviations: GCL, granule cell layer; H, hilus. **(b)** Unitary excitatory postsynaptic potentials (EPSPs) at a pyramidal neuron–interneuron synapse in the CA3 region (paired recording). The top trace shows a presynaptic (i.e. pyramidal neuron; PN) action potential and the middle trace shows a unitary EPSP in the postsynaptic interneuron (IN). The bottom trace shows the response of the postsynaptic interneuron to a depolarizing current pulse used to probe the membrane time constant. Recording temperature ≈37 °C. **(c)** Unitary excitatory postsynaptic currents (EPSCs) at the granule cell–basket cell synapse (paired recording). The top trace shows presynaptic action potential; the middle traces are individual evoked EPSCs in the postsynaptic basket cell (BC) and the bottom trace is an average EPSC. Recording temperature ≈34 °C. **(d)** Single-cell reverse transcription polymerase chain reaction (RT-PCR) analysis of AMPA receptor subunit expression in a dentate gyrus basket cell compared with a CA3 pyramidal neuron; differential hybridization of gels with selective radiolabeled oligonucleotide probes specific for GluR1 to GluR4 (GluR-A to GluR-D) AMPA receptor subunits is shown. Note low relative abundance of GluR2 (GluR-B) in the basket cell. Panels (a) and (c) reproduced, with permission, from Ref. [19]; (b) reproduced, with permission, from Ref [12]; (d) reproduced, with permission, from Ref. [24].

receptors are determined by the expression of an interneuron-specific genetic program. Unlike principal neuron AMPA receptors, which are often $GluR1_{flip}/GluR2_{flip}$ heteromers, basket cell AMPA receptors are primarily assembled from $GluR1_{flop}$ subunits [23,24], with GluR1 to GluR4 (GluR-A to GluR-D) indicating the four mammalian AMPA receptor subunits and flip and flop denoting the two variants of each subunit generated by alternative splicing (Figure 1d).

In addition to AMPA receptors, glutamate released at excitatory synapses on interneurons can coactivate kainate receptors and NMDA receptors [25]. Both types of receptor activate and deactivate more slowly than AMPA receptors: kainate receptors are gated on a timescale of tens of milliseconds [26,27], whereas NMDA receptors operate on a timescale of hundreds of milliseconds [25]. Thus, the different types of glutamate receptor could encode different features of afferent activity. For both kainate receptors and NMDA receptors, the amplitude contribution is highly variable. No kainate receptor component was observed in stratum radiatum interneurons in CA1 of the guinea pig [28]. By contrast, a significant kainate receptor component was found in EPSCs of oriens alveus interneurons and stratum radiatum interneurons in CA1 of the rat [26,27]. Likewise, a small NMDA receptor contribution was observed at mossy fiber–basket cell synapses of the dentate gyrus, at mossy fiber–stratum lucidum interneuron synapses in CA3, and in a subset of stratum radiatum interneurons in CA1 [19,29–31]. By contrast, a large contribution was found at pyramidal neuron–stratum lucidum interneuron synapses in CA3 and a different subset of stratum radiatum interneurons in CA1 [29,31]. Interestingly, the properties of AMPA receptor and NMDA receptor components are inversely correlated in CA3 stratum lucidum interneurons – a fast AMPA receptor component goes hand in hand with a small NMDA receptor component [29]. The correlation extends to the expression of receptor subunits – when AMPA receptors lack the GluR2 (GluR-B) subunit, NMDA receptors include the NR2B subunit. This co-regulation could arise at the level of gene expression, trafficking of subunit proteins to synapses, or via protein–protein interactions in the postsynaptic density [32].

Thus, glutamate-mediated excitation of interneurons involves an especially rapid AMPA receptor component, which ensures fast and reliable activation of inhibitory cells. Distinct contributions of slower kainate receptor and NMDA receptor components might confer specific

computational properties on different principal neuron–interneuron connections.

## Spatiotemporal signal processing in interneuron dendrites

Synaptic integration, in addition to depending on the time course of the postsynaptic conductance, depends on the dendritic location of the synapse and the cable properties of the dendrite [33,34]. In different interneuron subtypes, electron microscopical analysis suggests that 70–90% of synapses are excitatory [35]. The total population of excitatory synapses appears to be distributed uniformly over the somatodendritic domain, with 95–97% of synapses terminating on dendrites [35,36]. However, subsets of excitatory synapses originating from specific input pathways can be preferentially located on either proximal or distal dendritic locations [19,20].

How do interneuron dendrites process excitatory synaptic events? Locally, excitatory postsynaptic potential (EPSP) kinetics are similar to the time course of the postsynaptic conductance, and EPSP amplitude depends on synaptic peak conductance and dendritic impedance at the postsynaptic site [19,37–40]. As EPSPs propagate from the dendrites to the soma, their amplitude is attenuated and their time course is slowed. The EPSP decay approaches the membrane time constant ($\tau_m$) for long propagation distances but is faster and multi-exponential for intermediate propagation distances. The degree of filtering depends not only on synapse location but also on dendritic geometry and the specific resistance ($R_m$, resistance for a given membrane area) of the dendritic membrane. Several interneuron subtypes have a low input resistance and a fast $\tau_m$, suggesting a low $R_m$ (because $\tau_m = R_m C_m$, where $C_m$ is capacitance for a given membrane area [41–43]); this especially applies to parvalbumin-positive basket cells ($\tau_m$ ~10 ms). By contrast, principal cells have much higher input resistance and longer membrane time constant (~30–70 ms), implying a higher $R_m$ [44]. As a consequence of fast glutamate-mediated excitation and specific dendritic properties, the EPSP arriving at the interneuron soma has a relatively short half-duration (4–10 ms at physiological temperature) [12,19,45–50] (Figure 1b) compared with that in principal neurons [51]. At some principal neuron–interneuron synapses, the decay of the somatic unitary EPSP (as quantified by mono-exponential fit or amplitude-weighted average decay time constant) appears to be faster than the membrane time constant [12,19] (Figure 1b). This would be expected for a perisomatic synapse with a short EPSP propagation distance [19].

As the length constant of a passive dendritic cable is $\lambda = (rR_m/2R_i)^{0.5}$, where r is the radius and $R_i$ is cytoplasmic resistivity [33], a low $R_m$ implies that interneuron dendrites conduct voltage signals with strong attenuation. Although this might seem inefficient, the low $R_m$ has several advantages for signal processing. First, the short $\lambda$ limits postsynaptic interactions within the dendritic tree, leading to functional compartmentalization. Second, because the conduction velocity of a passive cylindrical cable approximates to $v = 2\lambda/\tau_m$ for the half-amplitude point of a propagating wave [33], the passive properties imply that interneuron dendrites conduct synaptic potentials slightly faster than those of principal neurons. Finally, the fast $\tau_m$ restricts temporal summation and assists coincidence detection, because the decay time course of the somatic EPSP is limited by $\tau_m$. In granule cell–basket cell synapses, the window for temporal summation of EPSPs is ~5 ms [19].

Thus, the low $R_m$ of the interneuron membrane shapes the spatiotemporal integration of synaptic input, leading to effective EPSP summation only for synchronous synaptic inputs.

## Tuning of resting membrane potential by neuromodulators

As first suggested by Eccles, interneurons are more excitable than principal cells [52]. More recent evidence suggests that this increased excitability is partly due to the relatively depolarized resting potential of interneurons, which sets them in a ready-to-fire mode. Both non-invasive cell-attached recordings [53,54] and conventional whole-cell techniques [42,43,55] revealed that the resting potential of different interneuron subtypes (e.g. basket cells and stratum radiatum interneurons) is ~10–15 mV more depolarized than that of pyramidal cells in the same circuit under comparable conditions, whereas the voltage thresholds for action potential initiation appear to be comparable. Several conductances contribute to the resting potential of interneurons and presumably to the different resting potentials of interneurons and principal cells. These include two-pore domain 'leak' $K^+$ channels [56–58], hyperpolarization-activated and cyclic-nucleotide-activated channels (HCN channels, also termed $I_h$) [59,60], G-protein-coupled inwardly rectifying $K^+$ (GIRK) channels [57], and low-threshold $Ca^{2+}$ channels [61]. Collectively, these conductances also represent the molecular basis of the low somatodendritic $R_m$, although the contribution of individual channels remains to be defined. A complete understanding of the molecular mechanisms of the interneuron resting potential also requires consideration of transporters, especially the electrogenic $Na^+/K^+$ pump [55].

Although the resting potential of interneurons is more depolarized than that of pyramidal neurons, it is regulated dynamically by ionotropic and metabotropic transmitter receptors (Figure 2). Various interneuron types express nicotinic ACh receptors [62,63] and ionotropic 5-hydroxytryptamine (5-HT) receptors [15]. Furthermore, CA1 stratum radiatum interneurons exhibit a tonic, picrotoxin-sensitive conductance mediated by extrasynaptic $GABA_A$ receptors, which appears to be absent in pyramidal neurons [64]. Finally, interneurons in hippocampus and neocortex also express a rich repertoire of metabotropic receptors for neurotransmitters, mainly with excitatory actions. These include muscarinic ACh receptors [65–67] (Figure 2a), metabotropic glutamate receptors [15,68] (Figure 2b), 5-HT receptors [15] (Figure 2c), adrenoceptors [69] (Figure 2d), $GABA_B$ receptors [70], opioid receptors [71], and dopamine receptors [57,72]. As a general rule, multiple metabotropic receptors can be coexpressed by a single interneuron [15] (Figure 2e) and a given receptor can affect multiple molecular targets, such as both two-pore domain channels and GIRK

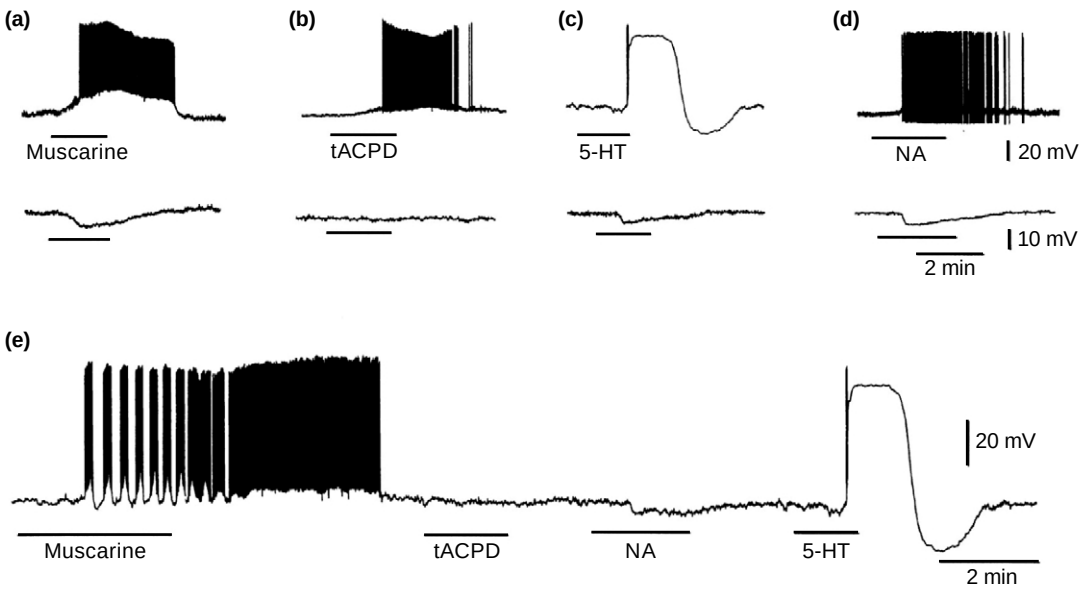


**Figure 2**. Diversity of expression of neurotransmitter receptors in hippocampal interneurons. **(a–d)** Examples of different responses of CA1 stratum radiatum interneurons to bath application of agonists of muscarinic ACh receptors (muscarine), metabotropic glutamate receptors [(1S,3R)-aminocyclopentane-1,3-dicarboxylic acid (tACPD)], 5-hydroxytryptamine receptors (5-HT), and adrenoceptors [noradrenaline (NA)]. Different cells show large diversity in the extent and direction of the responses, which were depolarizing (a–d, upper traces), null (b, lower trace) or hyperpolarizing (a,c,d, lower traces). **(e)** Responses of a single stratum radiatum interneuron to sequential application of several agonists. This cell was excited by muscarine and 5-HT, inhibited by noradrenaline and insensitive to tACPD. Reproduced, with permission, from Ref. [15].

channels [57]. The expression pattern of receptors and targets varies substantially among interneuron subtypes and among cells within the same subtype [15]. Thus, neuromodulatory transmitters can change excitability and integrative properties of specific subgroups of interneurons in the network, which can lead to the formation of flexible interneuron assemblies.

## Active conductances shape EPSPs and generate resonance behavior

Depending on both EPSP amplitude and resting potential, subthreshold active conductances will contribute to the high speed, reliability and temporal precision of EPSP–action potential coupling in interneurons (Figure 3). As in pyramidal neurons [73,74], activation of $Na^+$ channels amplifies subthreshold EPSPs in several interneuron subtypes [30,36,75]. Unlike in pyramidal neurons, however, activation of voltage-gated $K^+$ channels actively terminates EPSPs. This leads to EPSPs with largely voltage-independent time course in CA1 stratum radiatum interneurons [30] (Figure 3a) and to EPSPs with reduced duration at depolarized potentials in fast-spiking

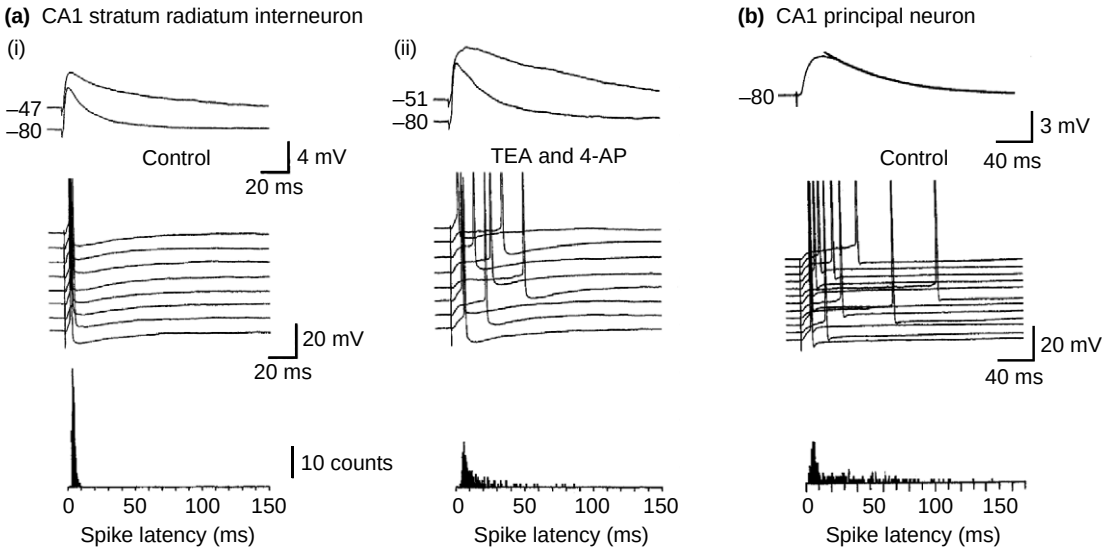


**Figure 3**. Speed and precision of excitatory postsynaptic potential (EPSP)–action potential coupling in hippocampal interneurons. **(a)** Evoked EPSPs in a stratum radiatum interneuron in the hippocampal CA1 region in control conditions (i) and in the presence of $K^+$ channel blockers 4-aminopyridine (4-AP, 40 μM) and tetraethylammonium (TEA, 1 mM) (ii). **(b)** Evoked EPSPs in a CA1 pyramidal cell in control conditions. Upper traces represent subthreshold EPSPs (averages); lower sets of traces show suprathreshold EPSPs recorded at depolarized resting potentials. Bottom panels show corresponding spike latency histograms. Note the precise timing of action potential generation in stratum radiatum interneurons under control conditions. Reproduced, with permission, from Ref. [30].

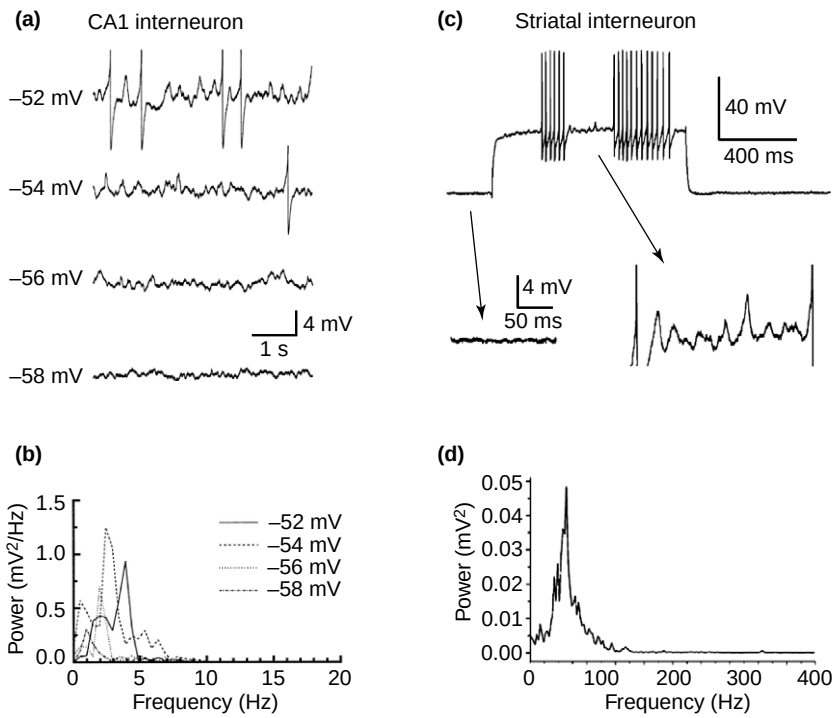


**Figure 4**. Subthreshold oscillations in the theta-frequency and gamma-frequency bands. **(a,b)** Intrinsic theta oscillations in lacunosum-moleculare interneurons in CA1. Membrane potential recordings are shown (mean values indicated) (a), with corresponding power spectra (b). The peak of the spectrum occurred roughly in the theta-frequency range (4–7 Hz). **(c,d)** Intrinsic gamma oscillations in fast-spiking interneurons in the striatum. Membrane potential oscillations are shown from periods in which no action potentials were generated (c), with the corresponding power spectrum (d). The peak of the spectrum occurred in the gamma-frequency range (30–90 Hz). Panels (a,b) reproduced, with permission, from Ref. [77]; (c,d) reproduced, with permission, from Ref. [79].

neocortical interneurons [75]. Thus, EPSPs in interneurons trigger action potentials more precisely than EPSPs in pyramidal cells [30] (Figure 3b). Experiments in which EPSP waveforms were applied as voltage-clamp commands revealed that subthreshold EPSPs activate a biphasic sequence of inward ($Na^+$)–outward ($K^+$) currents, which restricts the time window for spike initiation [30,75].

Subthreshold active conductances also confer resonance characteristics on interneurons (Figure 4). Several interneurons show oscillations during sustained current injection or application of depolarizing agonists [76–79], with frequencies in the theta (4–7 Hz; Figure 4a,b) or gamma (30–90 Hz; Figure 4c,d) ranges. These oscillations are apparently generated by the interplay of voltage-gated $Na^+$ channels and delayed-rectifier $K^+$ channels [76,77]. Furthermore, interneurons show subthreshold resonant behavior in response to sinusoidal inputs [78,80]. Finally, the reliability and temporal precision of action potential generation shows marked frequency dependence in response to repetitive suprathreshold inputs; the highest reliability and precision of spiking occurs at frequencies similar to those of the subthreshold oscillations [78–81]. Therefore, subthreshold oscillations and resonance behavior endow inhibitory interneurons with band-pass filter characteristics. The filter frequencies, however, differ markedly among interneuron types. Regularly spiking interneurons such as lacunosum-moleculare interneurons of the CA1 region show theta-frequency preference [76,77] (Figure 4a,b), whereas fast-spiking interneurons in hippocampus, neocortex and striatum oscillate at gamma frequencies [78,79] (Figure 4c,d). Thus, rhythmic input can recruit specific subsets of interneurons in neuronal networks. Although network oscillations are primarily driven by synaptic mechanisms, they can be enhanced by subthreshold oscillations and resonance phenomena, as described in the article by Whittington and Traub in this series [11].

## Molecular determinants of the fast-spiking phenotype

Mountcastle *et al.* [82] first described neocortical neurons with 'thin spikes' in extracellular recordings. McCormick *et al.* [83] identified cortical cells with brief action potentials as GABAergic neurons and showed that these could fire repetitively without accommodation at frequencies >200 Hz. However, subsequent analysis of different interneuron subtypes indicated that many, but not all, interneurons show this fast-spiking phenotype (Figure 5). Basket cells, hilar interneurons with axons co-aligned with the commissural–associational pathway (HICAP) cells in the dentate gyrus, and bistratified cells in CA1 and CA3 can all fire spikes at high frequency during sustained current injection (200–500 Hz at physiological temperature) [17,42,43] (Figure 5a). Oriens alveus interneurons were also categorized as 'fast spiking', although their maximal action potential frequency is closer to 100 Hz under similar experimental conditions [84–90]. Finally, other interneuron types, such as stratum radiatum and lacunosum-moleculare interneurons in the CA1 region, even show regular spiking with substantial accommodation [91], comparable to principal neurons. Thus, the action potential phenotype of interneurons is a spectrum,

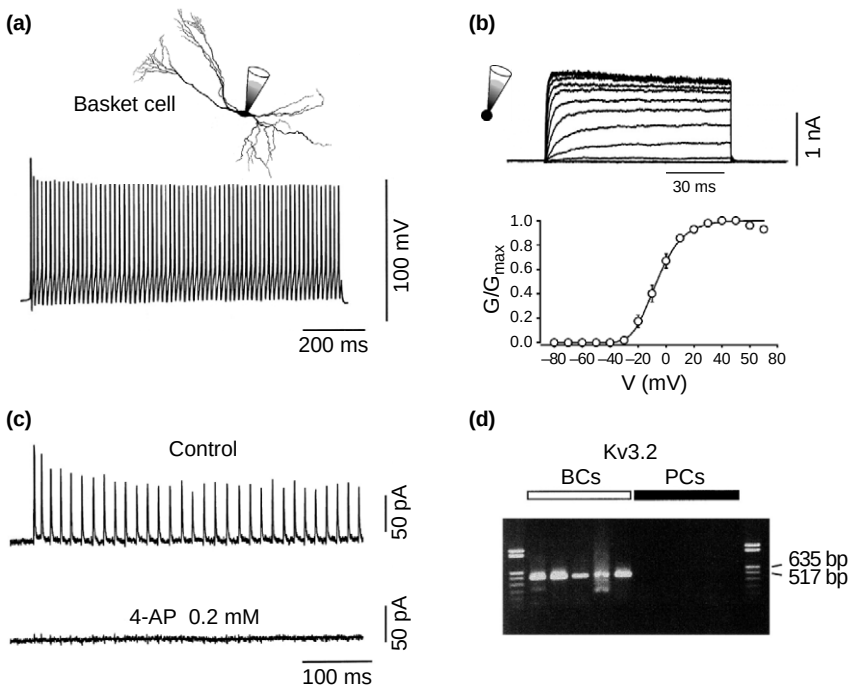


**Figure 5**. Kv3 channels – a major determinant of fast spiking. **(a)** Action potentials evoked by a 1 s depolarizing current pulse in a dentate gyrus basket cell. **(b)** Functional properties of Kv3-like delayed-rectifier $K^+$ channels. Upper graph: traces of $K^+$ current evoked by test pulses of stepwise increasing amplitude in a nucleated patch from a basket cell soma (inset). Lower graph: plot of conductance ratio ($G/G_{max}$) against membrane potential. The Kv3 component was isolated by pharmacological subtraction. **(c)** $K^+$ current in a basket cell nucleated patch during a high-frequency train of action potentials. An experimentally recorded action potential pattern was applied as a voltage-clamp command, and the resulting $K^+$ current was measured in the absence (top trace) and in the presence (bottom trace) of 4-aminopyridine (4-AP, 0.2 mM). **(d)** Single-cell reverse transcription polymerase chain reaction (RT-PCR) analysis of Kv3 subunit expression in dentate gyrus basket cells and CA1 pyramidal neurons. Ethidium bromide-stained gels of the RT-PCR products amplified with primers specific for Kv3.2 transcripts. Left lanes show material from basket cells (BCs); right lanes show that from pyramidal cells (PCs). Reproduced, with permission, from Ref [87], © (1998) the Society for Neuroscience.

with parvalbumin-positive basket cells representing the functional extreme.

Action potentials of fast-spiking interneurons are succeeded by a fast, large-amplitude afterhyperpolarization (AHP) [83,92]. This might seem counter-intuitive, as a large AHP would be expected to delay the onset of the next spike and thus reduce the firing frequency [93]. How should an AHP accelerate action potential initiation? The kinetics of the AHP appear to be optimal for a maximal recovery of $Na^+$ channels from inactivation and a minimal delay in the onset of the action potential initiation [90,94]. A shorter AHP, by contrast, would not permit sufficient recovery of $Na^+$ channels from inactivation, leading to longer refractory periods.

Which channels underlie the fast-spiking phenotype? Although the properties of both $Na^+$ channels [94] and voltage-gated $K^+$ channels [85–87,89] differ between interneurons and principal cells, the characteristic action potential pattern of interneurons is largely shaped by the $K^+$ channels. $K^+$ currents in basket cells of the dentate gyrus and oriens alveus interneurons include fast delayed-rectifier, slow delayed-rectifier, inactivating A-type and $Ca^{2+}$-activated $K^+$ currents [85–87,89]. The fast delayed rectifier forms a large part of the macroscopic $K^+$ current for both types of interneuron (Figure 5b). It contributes ~60% of responses to rectangular stimuli, and >90% of responses to action-potential-like voltage-clamp commands [87] (Figure 5c). Immunocytochemical and single-cell reverse transcription polymerase chain reaction (RT-PCR) analysis revealed that the channels mediating the fast delayed rectifier $K^+$ current are assembled from Kv3 subunits, particularly Kv3.1 and Kv3.2 [87,89,95–99] (Figure 5d). Thus, the characteristic action potential phenotype results from an interneuron-specific genetic program. How do Kv3 channels facilitate fast spiking? Dynamic-clamp experiments in which artificial $K^+$ conductances were added to real neurons [90,100] revealed that the gating properties of Kv3 channels, in particular fast deactivation, high activation threshold and lack of inactivation, are crucial for fast spiking. By contrast, a low activation threshold leads to adaptation, and an inactivation process leads to action potential broadening; these are hallmarks of action potential phenotypes of principal cells [90]. As both density and gating properties of Kv3 channels are regulated by gene expression and phosphorylation [89,97,101], differential tuning of Kv3 channels could contribute to the differences in firing properties between interneuron types.

Thus, many interneurons discharge brief action potentials at high frequencies without accommodation during long-lasting stimulation. Kv3 channels appear to be necessary for the fast-spiking phenotype, and their gating properties favor high-frequency action potential generation.

## Active dendritic propagation of action potentials

In pyramidal neurons, EPSPs propagate from the dendrite to the soma and the axon initial segment, the primary site of integration and action potential initiation [102]. By contrast, interneurons can use a different signaling strategy (Figure 6). First, in some interneuron subtypes

the axon emerges from a principal dendrite rather than the soma. Dendritic origin of the axon, first described in GABAergic neurons of the substantia nigra [103], has been reported for oriens alveus interneurons in the hippocampal CA1 region [36] (Figure 6a) and somatostatin-positive bipolar interneurons in the neocortex [104]. Second, the dendrites of some interneuron subtypes have active properties, supporting action potential backpropagation and dendritic action potential initiation [36] (Figure 6b–d). Both the dendritic emergence of the axon and the active properties of interneuron dendrites can speed up EPSP–action potential conversion.

Active properties of interneuron dendrites were first postulated on theoretical grounds [105] and more recently have been demonstrated directly using dendritic recordings. These experiments revealed that the dendrites of oriens alveus interneurons in the CA1 region of the hippocampus express a high density of voltage-gated $Na^+$ and $K^+$ channels; the estimated $Na^+$ conductance density was ~110 pS $\mu m^{-2}$ [36] (Figure 6b), approximately threefold larger than in principal neuron dendrites [102]. Furthermore, dendritic recordings showed that action potentials in both oriens alveus interneurons in hippocampus and somatostatin-positive interneurons in neocortex can be initiated at multiple sites and propagate over the somatodendritic domain with constant amplitude and time course [36,104] (Figure 6c). $Ca^{2+}$-imaging experiments confirmed the active properties of interneuron dendrites [104,106]; action-potential-induced dendritic $Ca^{2+}$ transients showed large amplitudes for distances of up to 400 μm from the soma in somatostatin-positive neocortical interneurons [104] (Figure 6d). Thus, voltage-gated $Na^+$ channels apparently dominate the functional properties of dendrites of these interneurons, supporting the active dendritic propagation of action potentials. By contrast, action-potential-induced $Ca^{2+}$ transients declined as a function of distance from the soma in parvalbumin- and calretinin-positive neocortical interneurons [106],

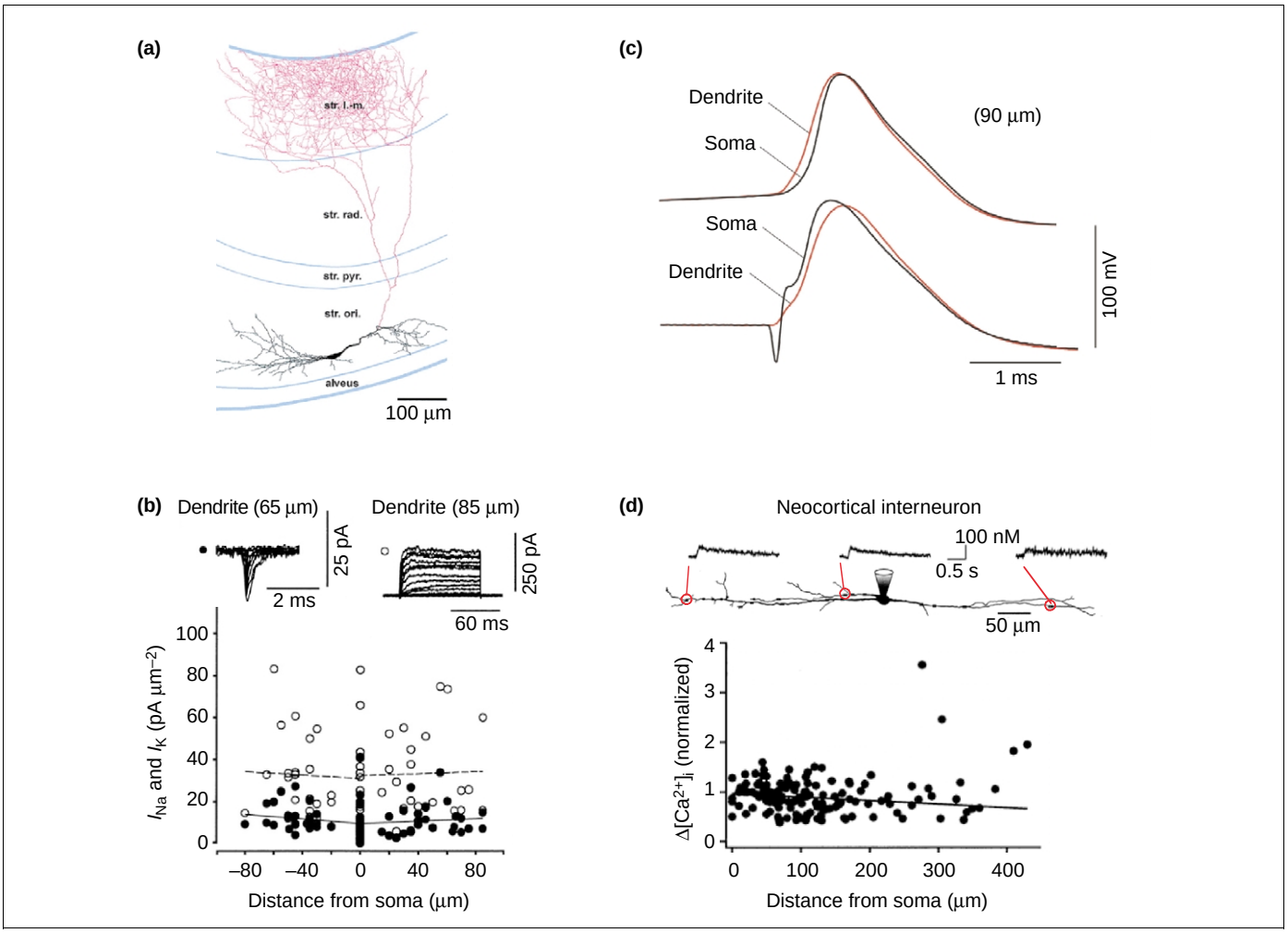


**Figure 6**. Active dendrites in somatostatin-positive interneuron subtypes. **(a)** Morphological reconstruction of an oriens alveus interneuron in the hippocampal CA1 region (soma and dendrites, black; axon, red). Abbreviations: str. l.-m., stratum lacunosum-moleculare; str. ori., stratum oriens; str. pyr., stratum pyramidale; str. rad., stratum radiatum. **(b)** $Na^+$ (solid symbols and continuous lines) and $K^+$ (open symbols and broken lines) current densities, calculated from maximal inward or outward current at −10 mV and plotted against distance from the soma; positive values indicate the axon-bearing dendrite. $Na^+$ and $K^+$ current traces are shown as insets. **(c)** Swapping of action potential initiation between dendrite and soma. Simultaneous current-clamp recordings from dendrite (red traces) and soma (black traces) in an oriens alveus interneuron. Action potential initiation was close to the dendritic recording site with a long pulse of low intensity (upper traces), but was shifted towards the somatic recording site with a brief pulse of high intensity (lower traces). Numbers in (b) and (c) indicate dendritic recording distances. **(d)** Active dendrites in neocortical bitufted neurons. Dependence on distance from the soma of the peak amplitude of intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) transients evoked by four action potentials at 80 Hz. Data were normalized to the amplitude of the dendritic $[Ca^{2+}]_i$ transient closest to the soma. Reconstruction of bitufted neuron and examples of $[Ca^{2+}]_i$ transients are shown as insets. Panels (a–c) reproduced, with permission from, Ref. [36]; (d) reproduced, with permission, from Ref. [104].

indicating that voltage-gated $K^+$ channels could actively inhibit the dendritic propagation of action potentials in these interneurons.

In addition to acceleration of EPSP–action potential conversion, active conductances in interneuron dendrites could serve several other functions. They might reduce location-dependent variability in action potential initiation in response to different spatial patterns of synaptic inputs [107] and facilitate retrograde propagation of action potentials from the soma into the dendrites [36,104]. Backpropagated action potentials potentially contribute to the induction of plasticity at glutamatergic synapses on interneurons [108,109] and could trigger the release of GABA and other retrograde messengers from interneuron dendrites [110].

## Synchronous GABA release at interneuron output synapses

Once initiated, interneuron action potentials propagate along the axon and trigger GABA release from inhibitory terminals (Figure 7). The reliability of impulse conduction in morphologically complex interneuron axons is unknown. However, both the high release probability at the basket cell–granule cell synapse in the dentate gyrus [111] and the reliability of action-potential-evoked $Ca^{2+}$ signals in axons of cerebellar interneurons [112] suggest that conduction failures are rare. Kainate increases axonal excitability of stratum radiatum interneurons in CA1 [28], suggesting that kainate receptors regulate impulse conduction via depolarization of the axon. The shape of presynaptic action potentials that trigger $Ca^{2+}$ inflow and transmitter release at inhibitory terminals has not been measured directly [113]. However, the highly synchronized GABA release at the basket cell–granule cell synapse in the dentate gyrus (half-duration of the time course of quantal release is ~300 μs at 34°C; Figure 7b,c) suggests that they might even be shorter than somatic spikes [111].

In addition to forming inhibitory synapses on principal neurons, interneurons also form synaptic contacts onto each other [114–119]. After all previous considerations, it might not come as a surprise that the synaptic communication among interneurons is particularly optimized for speed. In comparison with interneuron–principal neuron synapses, two major differences of interneuron–interneuron synapses are apparent. First, mutual synaptic inhibition between hippocampal and neocortical interneurons is mediated by both electrical and chemical synapses [114–119]. Because electrical coupling is mediated by perisomatic gap junctions [120], the time course of the electrical postsynaptic currents is fast, following the

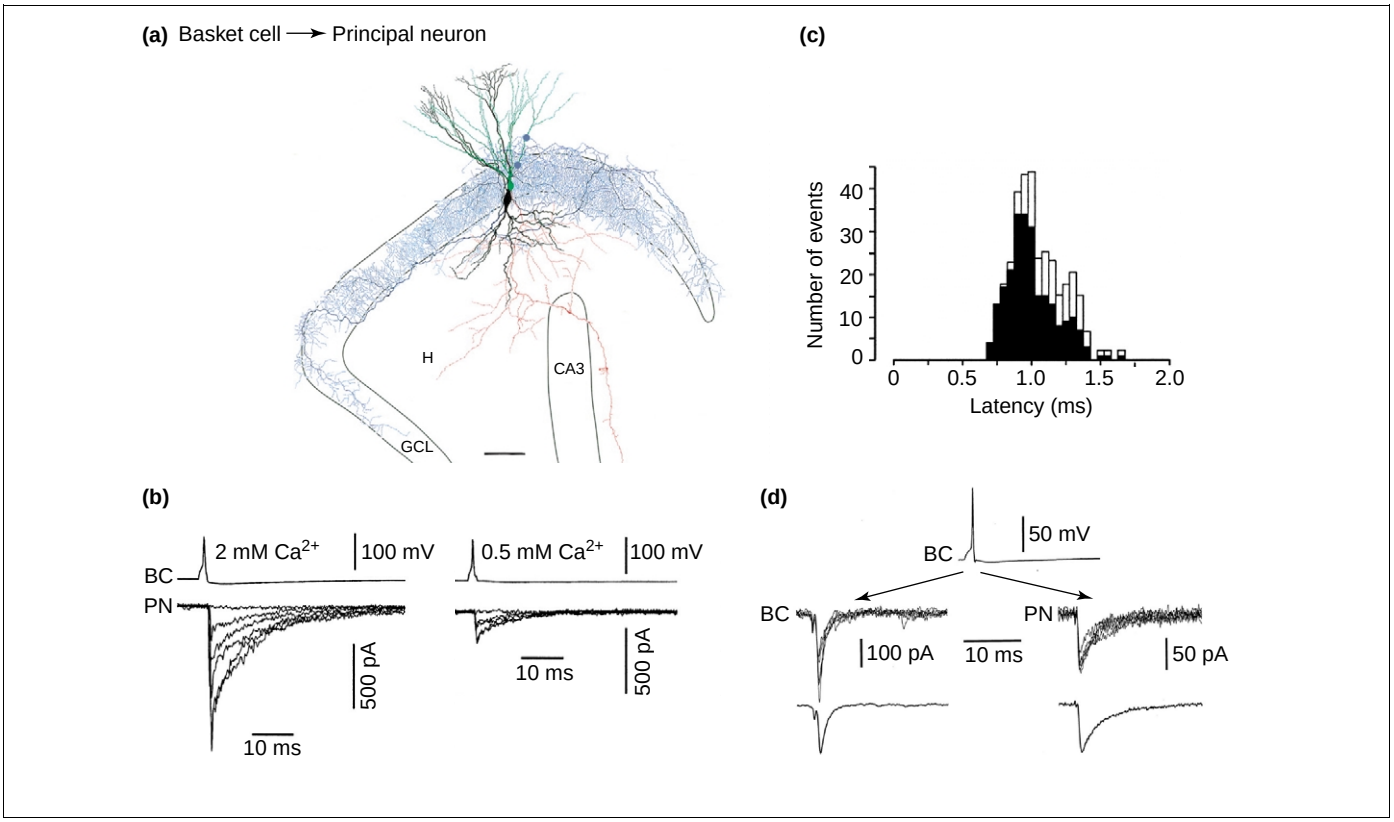


**Figure 7**. Fast signaling at GABAergic interneuron output synapses. **(a)** Morphological reconstruction of a reciprocally coupled granule cell (i.e. principal neuron; soma and dendrites, green; axon, red) and basket cell (soma and dendrites, black; axon, blue) pair (the same neurons as shown in Figure 1). Two putative inhibitory synaptic contacts (blue dots) are shown. **(b)** Recording of unitary inhibitory postsynaptic currents (IPSCs) at the basket cell (BC)–granule cell (PN) synapse at different $Ca^{2+}$ and $Mg^{2+}$ concentrations (2 mM $Ca^{2+}$; 1 mM $Mg^{2+}$ and 0.5 mM $Ca^{2+}$; 2.5 mM $Mg^{2+}$). **(c)** Time course of quantal release at the basket cell–granule cell synapse. First latency distribution (filled bars) and time course of quantal release (open bars), calculated from first latencies in 0.5 mM $Ca^{2+}$ and 2.5 mM $Mg^{2+}$. **(d)** Synchrony of GABA release is independent of the nature of the postsynaptic target cell, whereas the IPSC decay time constant is target-cell-dependent. Sequential triple recording from a presynaptic and a postsynaptic basket cell (left traces, first pair) and the same presynaptic basket cell and a postsynaptic granule cell (right traces, second pair). Presynaptic action potentials (top), single unitary IPSCs (center) and average IPSC (bottom) are depicted. Note the difference in decay time course. Also note the fast current component due to gap-junction coupling in the basket cell–basket cell connection. Panel (a) reproduced, with permission, from Ref [19]; (b) and (c) reproduced, with permission, from Ref [111], © (2000) the Society for Neuroscience; (d) reproduced, with permission, from Ref [114], © (2001) the Society for Neuroscience.

time course of the presynaptic action potential. Second, the time course of the GABA-mediated inhibitory postsynaptic currents (IPSCs) in hippocampal interneurons and neocortical fast-spiking interneurons is markedly faster than the kinetics of IPSCs in principal neurons of the same circuit [6,114,117] (Figure 7d). Thus, if two interneurons are coupled via both electrical and chemical synapses, an action potential in the presynaptic interneuron triggers a biphasic sequence of excitatory (inward)–inhibitory (outward) currents in the postsynaptic cell, promoting precise, synchronous action potential initiation.

Both electrical and chemical synaptic signaling between interneurons are crucial for network activity. Electrical coupling can selectively regulate the coherence of high-frequency network oscillations, whereas the time course of the chemical $GABA_A$-receptor-mediated component can control both coherence and frequency [6]. Furthermore, both electrical coupling between interneurons and disynaptic feedforward inhibition (i.e. principal neurons excite an interneuron, which inhibits another interneuron) will promote synchrony detection in interneuron networks [75], amplifying the fast signaling processes present at the level of a single cell. The early excitatory electrical component will boost synchronous EPSPs, whereas the later inhibitory postsynaptic potential (IPSP) will suppress asynchronous events. Thus, interneurons in the network can ultimately detect synchronous excitatory activity with ~1 ms precision [75].

## Concluding remarks

In both hippocampal and neocortical microcircuits, GABAergic interneurons differ radically from glutamatergic principal cells. Some of the properties of interneurons are reminiscent of neurons in the auditory pathway, where temporal precision is crucial for sound localization. Remarkable similarities between interneurons and auditory neurons include the expression of special AMPA receptors mediating fast synaptic excitation, the rapid membrane time constant, and the expression of Kv3 channels [121,122]. Together with other interneuron-specific mechanisms, these properties ensure that inhibitory interneurons operate with high speed, reliability and precision. This is likely to be necessary for the generation of precise signals for temporal coding of information in the brain and for the control over spike-timing-dependent plasticity at glutamatergic synapses [123–125].

### Acknowledgements

We thank Marlene Bartos, Jan Behrends, Michael Häusser, Manfred Heckmann, Chris McBain, Jean-Christophe Poncer, Greg Stuart and Imre Vida for reading previous versions of the manuscript. Work of the authors was supported by the Deutsche Forschungsgemeinschaft, the Alexander-von-Humboldt Foundation, the Human Frontiers Science Program Organization, INSERM, the National Institutes of Health (MH54671), and the Ministère de la Recherche

### References

1 Cobb, S.R. *et al.* (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* 378, 75–78
2 Pouille, F. and Scanziani, M. (2001) Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. *Science* 293, 1159–1163
3 Miles, R. *et al.* (1996) Differences between somatic and dendritic inhibition in the hippocampus. *Neuron* 16, 815–823
4 Whittington, M.A. *et al.* (1995) Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature* 373, 612–615
5 Wang, X-J. and Buzsáki, G. (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* 16, 6402–6413
6 Bartos, M. *et al.* (2002) Fast synaptic inhibition promotes synchronized gamma oscillations in hippocampal interneuron networks. *Proc. Natl. Acad. Sci. U. S. A.* 99, 13222–13227
7 Bragin, A. *et al.* (1995) Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* 15, 47–60
8 Ylinen, A. *et al.* (1995) Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: Network and intracellular mechanisms. *J. Neurosci.* 15, 30–46
9 Klausberger, T. *et al.* (2003) Brain-state- and cell-type-specific firing of hippocampal interneurons *in vivo*. *Nature* 421, 844–848
10 Buzsáki, G. and Henze, D. *Interneuron Diversity series*: GABAergic systems *in vivo*. *Trends Neurosci*. (in press)
11 Whittington, M.A. and Traub, R.D. (2003) *Interneuron Diversity series*: Inhibitory interneurons and network oscillations *in vitro*. *Trends Neurosci.* doi:10.1016/j.tins.2003.09.016
12 Miles, R. (1990) Synaptic excitation of inhibitory cells by single CA3 hippocampal pyramidal cells of the guinea-pig *in vitro*. *J. Physiol.* 428, 61–77
13 Csicsvari, J. *et al.* (1998) Reliability and state dependence of pyramidal cell–interneuron synapses in the hippocampus: an ensemble approach in the behaving rat. *Neuron* 21, 179–189
14 Carter, A.G. and Regehr, W.G. (2002) Quantal events shape cerebellar interneuron firing. *Nat. Neurosci.* 5, 1309–1318
15 Parra, P. *et al.* (1998) How many subtypes of inhibitory cells in the hippocampus? *Neuron* 20, 983–993
16 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
17 Han, Z-S. *et al.* (1993) A high degree of spatial selectivity in the axonal and dendritic domains of physiologically identified local-circuit neurons in the dentate gyrus of the rat hippocampus. *Eur. J. Neurosci.* 5, 395–410
18 Sik, A. *et al.* (1995) Hippocampal CA1 interneurons: an *in vivo* intracellular labeling study. *J. Neurosci.* 15, 6651–6665
19 Geiger, J.R.P. *et al.* (1997) Submillisecond AMPA receptor-mediated signaling at a principal neuron–interneuron synapse. *Neuron* 18, 1009–1023
20 Walker, H.C. *et al.* (2002) Activation of kinetically distinct synaptic conductances on inhibitory interneurons by electrotonically overlapping afferents. *Neuron* 35, 161–171
21 Jonas, P. *et al.* (1993) Quantal components of unitary EPSCs at the mossy fibre synapse on CA3 pyramidal cells of rat hippocampus. *J. Physiol.* 472, 615–663
22 Vida, I. and Frotscher, M. (2000) A hippocampal interneuron associated with the mossy fiber system. *Proc. Natl. Acad. Sci. U. S. A.* 97, 1275–1280
23 Lawrence, J.J. and McBain, C.J. (2003) Interneuron Diversity series: Containing the detonation – feedforward inhibition in the CA3 hippocampus. *Trends Neurosci.* doi:10.1016/j.tins.2003.09.007
24 Geiger, J.R.P. *et al.* (1995) Relative abundance of subunit mRNAs determines gating and $Ca^{2+}$ permeability of AMPA receptors in principal neurons and interneurons in rat CNS. *Neuron* 15, 193–204
25 Bekkers, J.M. and Stevens, C.F. (1989) NMDA and non-NMDA receptors are co-localized at individual excitatory synapses in cultured rat hippocampus. *Nature* 341, 230–233
26 Cossart, R. *et al.* (1998) GluR5 kainate receptor activation in interneurons increases tonic inhibition of pyramidal cells. *Nat. Neurosci.* 1, 470–478
27 Frerking, M. *et al.* (1998) Synaptic activation of kainate receptors on hippocampal interneurons. *Nat. Neurosci.* 1, 479–486
28 Semyanov, A. and Kullmann, D.M. (2001) Kainate receptor-dependent axonal depolarization and action potential initiation in interneurons. *Nat. Neurosci.* 4, 718–723
29 Lei, S. and McBain, C.J. (2002) Distinct NMDA receptors provide

differential modes of transmission at mossy fiber–interneuron synapses. *Neuron* 33, 921–933
30 Fricker, D. and Miles, R. (2000) EPSP amplification and the precision of spike timing in hippocampal neurons. *Neuron* 28, 559–569
31 Maccaferri, G. and Dingledine, R. (2002) Control of feedforward dendritic inhibition by NMDA receptor-dependent spike timing in hippocampal interneurons. *J. Neurosci.* 22, 5462–5472
32 Bischofberger, J. and Jonas, P. (2002) TwoB or not twoB: Differential transmission at glutamatergic mossy fiber–interneuron synapses in the hippocampus. *Trends Neurosci.* 25, 600–603
33 Jack, J.J.B. *et al.* (1983) *Electric Current Flow in Excitable Cells*, Clarendon Press
34 Johnston, D. and Wu, S.M-S. (1995) *Foundations of Cellular Neurophysiology*, MIT Press
35 Gulyás, A.I. *et al.* (1999) Total number and ratio of excitatory and inhibitory synapses converging onto single interneurons of different types in the CA1 area of the rat hippocampus. *J. Neurosci.* 19, 10082–10097
36 Martina, M. *et al.* (2000) Distal initiation and active propagation of action potentials in interneuron dendrites. *Science* 287, 295–300
37 Softky, W. (1994) Sub-millisecond coincidence detection in active dendritic trees. *Neuroscience* 58, 13–41
38 Stuart, G. *et al.* (1999) *Dendrites*, Oxford University Press
39 Geiger, J.R.P. *et al.* (1999) Glutamate-mediated synaptic excitation of cortical interneurons. In *Ionotropic Glutamate Receptors in the CNS. Handbook of Experimental Pharmacology* (Vol. 141) (Jonas, P. and Monyer, H., eds), pp. 363–398, Springer
40 Emri, Z.S. *et al.* (2001) Electrotonic profile and passive propagation of synaptic potentials in three subpopulations of hippocampal CA1 interneurons. *Neuroscience* 104, 1013–1026
41 Morin, F. *et al.* (1996) Membrane properties and synaptic currents evoked in CA1 interneuron subtypes in rat hippocampal slices. *J. Neurophysiol.* 76, 1–16
42 Mott, D.D. *et al.* (1997) Interneurons of the dentate–hilus border of the rat dentate gyrus: morphological and electrophysiological heterogeneity. *J. Neurosci.* 17, 3990–4005
43 Lübke, J. *et al.* (1998) Specialized electrophysiological properties of anatomically identified neurons in the hilar region of the rat fascia dentata. *J. Neurophysiol.* 79, 1518–1534
44 Spruston, N. and Johnston, D. (1992) Perforated patch-clamp analysis of the passive membrane properties of three classes of hippocampal neurons. *J. Neurophysiol.* 67, 508–529
45 Scharfman, H.E. *et al.* (1990) Synaptic connections of dentate granule cells and hilar neurons: results of paired intracellular recordings and intracellular horseradish peroxidase injections. *Neuroscience* 37, 693–707
46 Debanne, D. *et al.* (1995) Physiology and pharmacology of unitary synaptic connections between pairs of cells in areas CA3 and CA1 of rat hippocampal slice cultures. *J. Neurophysiol.* 73, 1282–1294
47 Buhl, E.H. *et al.* (1997) Effect, number and location of synapses made by single pyramidal cells onto aspiny interneurones of cat visual cortex. *J. Physiol.* 500, 689–713
48 Lacaille, J-C. *et al.* (1987) Local circuit interactions between oriens/alveus interneurons and CA1 pyramidal cells in hippocampal slices: electrophysiology and morphology. *J. Neurosci.* 7, 1979–1993
49 Ali, A.B. and Thomson, A.M. (1998) Facilitating pyramid to horizontal oriens-alveus interneurone inputs: dual intracellular recordings in slices of rat hippocampus. *J. Physiol.* 507, 185–199
50 Angulo, M.C. *et al.* (1999) Postsynaptic glutamate receptors and integrative properties of fast-spiking interneurons in the rat neocortex. *J. Neurophysiol.* 82, 1295–1302
51 Markram, H. *et al.* (1997) Physiology and anatomy of synaptic connections between thick tufted pyramidal neurones in the developing rat neocortex. *J. Physiol.* 500, 409–440
52 Eccles, J.C. (1969) *The Inhibitory Pathways of the Central Nervous System*, Liverpool University Press
53 Fricker, D. *et al.* (1999) Cell-attached measurements of the firing threshold of rat hippocampal neurones. *J. Physiol.* 517, 791–804
54 Verheugen, J.A.H. *et al.* (1999) Noninvasive measurements of the membrane potential and GABAergic action in hippocampal interneurons. *J. Neurosci.* 19, 2546–2555
55 Ross, S.T. and Soltesz, I. (2000) Selective depolarization of interneurons in the early posttraumatic dentate gyrus: Involvement of the $Na^+/K^+$-ATPase. *J. Neurophysiol.* 83, 2916–2930
56 Koh, D-S. *et al.* (1992) A TEA-insensitive flickering potassium channel active around the resting potential in myelinated nerve. *J. Membr. Biol.* 130, 149–162
57 Gorelova, N. *et al.* (2002) Mechanisms of dopamine activation of fast-spiking interneurons that exert inhibition in rat prefrontal cortex. *J. Neurophysiol.* 88, 3150–3166
58 Goldstein, S.A.N. *et al.* (2001) Potassium leak channels and the KCNK family of two-P-domain subunits. *Nat. Rev. Neurosci.* 2, 175–184
59 Maccaferri, G. and McBain, C.J. (1996) The hyperpolarization-activated current ($I_h$) and its contribution to pacemaker activity in rat CA1 hippocampal stratum oriens-alveus interneurones. *J. Physiol.* 497, 119–130
60 Lupica, C.R. *et al.* (2001) Contribution of the hyperpolarization-activated current ($I_h$) to membrane potential and GABA release in hippocampal interneurons. *J. Neurophysiol.* 86, 261–268
61 Fraser, D.D. and MacVicar, B.A. (1991) Low-threshold transient calcium current in rat hippocampal lacunosum-moleculare interneurons: kinetics and modulation by neurotransmitters. *J. Neurosci.* 11, 2812–2820
62 Jones, S. and Yakel, J.L. (1997) Functional nicotinic ACh receptors on interneurones in the rat hippocampus. *J. Physiol.* 504, 603–610
63 McQuiston, A.R. and Madison, D.V. (1999) Nicotinic receptor activation excites distinct subtypes of interneurons in the rat hippocampus. *J. Neurosci.* 19, 2887–2896
64 Semyanov, A. *et al.* (2003) GABA uptake regulates cortical excitability via cell type-specific tonic inhibition. *Nat. Neurosci.* 6, 484–490
65 McQuiston, A.R. and Madison, D.V. (1999) Muscarinic receptor activity has multiple effects on the resting membrane potentials of CA1 hippocampal interneurons. *J. Neurosci.* 19, 5693–5702
66 Behrends, J.C. and ten Bruggencate, G. (1993) Cholinergic modulation of synaptic inhibition in the guinea pig hippocampus in vitro: Excitation of GABAergic interneurons and inhibition of GABA-release. *J. Neurophysiol.* 69, 626–629
67 Hájos, N. *et al.* (1998) Distinct interneuron types express M2 muscarinic receptor immunoreactivity on their dendrites or axon terminals in the hippocampus. *Neuroscience* 82, 355–376
68 McBain, C.J. *et al.* (1994) Activation of metabotropic glutamate receptors differentially affects two classes of hippocampal interneurons and potentiates excitatory synaptic transmission. *J. Neurosci.* 14, 4433–4445
69 Bergles, D.E. *et al.* (1996) Excitatory actions of norepinephrine on multiple classes of hippocampal CA1 interneurons. *J. Neurosci.* 16, 572–585
70 Mott, D.D. *et al.* (1999) $GABA_B$-receptor-mediated currents in interneurons of the dentate–hilus border. *J. Neurophysiol.* 82, 1438–1450
71 Svoboda, K.R. and Lupica, C.R. (1998) Opioid inhibition of hippocampal interneurons via modulation of potassium and hyperpolarization-activated cation ($I_h$) currents. *J. Neurosci.* 18, 7084–7098
72 Zhou, F-M. and Hablitz, J.J. (1999) Dopamine modulation of membrane and synaptic properties of interneurons in rat cerebral cortex. *J. Neurophysiol.* 81, 967–976
73 Magee, J.C. and Johnston, D. (1995) Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. *Science* 268, 301–304
74 Stuart, G. and Sakmann, B. (1995) Amplification of EPSPs by axosomatic sodium channels in neocortical pyramidal neurons. *Neuron* 15, 1065–1076
75 Galarreta, M. and Hestrin, S. (2001) Spike transmission and synchrony detection in networks of GABAergic interneurons. *Science* 292, 2295–2299
76 Chapman, C.A. and Lacaille, J-C. (1999) Cholinergic induction of theta-frequency oscillations in hippocampal inhibitory interneurons and pacing of pyramidal cell firing. *J. Neurosci.* 19, 8637–8645
77 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
78 Fellous, J-M. *et al.* (2001) Frequency dependence of spike timing reliability in cortical pyramidal cells and interneurons. *J. Neurophysiol.* 85, 1782–1787

79 Bracci, E. *et al.* (2003) Voltage-dependent membrane potential oscillations of rat striatal fast-spiking interneurons. *J. Physiol.* 549, 121–130

80 Pike, F.G. *et al.* (2000) Distinct frequency preferences of different types of rat hippocampal neurones in response to oscillatory input currents. *J. Physiol.* 529, 205–213

81 Richardson, M.J.E. *et al.* (2003) From subthreshold to firing-rate resonance. *J. Neurophysiol.* 89, 2538–2554

82 Mountcastle, V.B. *et al.* (1969) Cortical neuronal mechanisms in flutter-vibration, studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination. *J. Neurophysiol.* 32, 452–484

83 McCormick, D.A. *et al.* (1985) Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. *J. Neurophysiol.* 54, 782–806

84 Lacaille, J-C. and Williams, S. (1990) Membrane properties of interneurons in stratum oriens-alveus of the CA1 region of rat hippocampus *in vitro*. *Neuroscience* 36, 349–359

85 Zhang, L. and McBain, C.J. (1995) Voltage-gated potassium currents in stratum oriens-alveus inhibitory neurones of the rat CA1 hippocampus. *J. Physiol.* 488, 647–660

86 Zhang, L. and McBain, C.J. (1995) Potassium conductances underlying repolarization and afterhyperpolarization in rat CA1 hippocampal interneurones. *J. Physiol.* 488, 661–672

87 Martina, M. *et al.* (1998) Functional and molecular differences between voltage-gated $K^+$ channels of fast-spiking interneurons and pyramidal neurons of rat hippocampus. *J. Neurosci.* 18, 8111–8125

88 Oliva, A.A. Jr *et al.* (2000) Novel hippocampal interneuronal subtypes identified using transgenic mice that express green fluorescent protein in GABAergic interneurons. *J. Neurosci.* 20, 3354–3368

89 Lien, C-C. *et al.* (2002) Gating, modulation and subunit composition of voltage-gated $K^+$ channels in dendritic inhibitory interneurones of rat hippocampus. *J. Physiol.* 538, 405–419

90 Lien, C-C. and Jonas, P. (2003) Kv3 potassium conductance is necessary and kinetically optimized for high-frequency action potential generation in hippocampal interneurons. *J. Neurosci.* 23, 2058–2068

91 Lacaille, J-C. and Schwartzkroin, P.A. (1988) Stratum lacunosum-moleculare interneurons of hippocampal CA1 region. I. Intracellular response characteristics, synaptic responses, and morphology. *J. Neurosci.* 8, 1400–1410

92 Connors, B.W. and Gutnick, M.J. (1990) Intrinsic firing patterns of diverse neocortical neurons. *Trends Neurosci.* 13, 99–104

93 Hille, B. (2001) *Ion Channels of Excitable Membranes*, 3rd edn, Sinauer

94 Martina, M. and Jonas, P. (1997) Functional differences in $Na^+$ channel gating between fast-spiking interneurones and principal neurones in rat hippocampus. *J. Physiol.* 505, 593–603

95 Du, J. *et al.* (1996) Developmental expression and functional characterization of the potassium-channel subunit Kv3.1b in parvalbumin-containing interneurons of the rat hippocampus. *J. Neurosci.* 16, 506–518

96 Erisir, A. *et al.* (1999) Function of specific $K^+$ channels in sustained high-frequency firing of fast-spiking neocortical interneurons. *J. Neurophysiol.* 82, 2476–2489

97 Atzori, M. *et al.* (2000) $H_2$ histamine receptor-phosphorylation of Kv3.2 modulates interneuron fast spiking. *Nat. Neurosci.* 3, 791–798

98 Lau, D. *et al.* (2000) Impaired fast-spiking, suppressed cortical inhibition, and increased susceptibility to seizures in mice lacking Kv3.2 $K^+$ channel proteins. *J. Neurosci.* 20, 9071–9085

99 Rudy, B. and McBain, C.J. (2001) Kv3 channels: voltage-gated $K^+$ channels designed for high-frequency repetitive firing. *Trends Neurosci.* 24, 517–526

100 Ma, M. and Koester, J. (1996) The role of $K^+$ currents in frequency-dependent spike broadening in *Aplysia* R20 neurons: A dynamic-clamp analysis. *J. Neurosci.* 16, 4089–4101

101 Macica, C.M. and Kaczmarek, L.K. (2001) Casein kinase 2 determines the voltage dependence of the Kv3.1 channel in auditory neurons and transfected cells. *J. Neurosci.* 21, 1160–1168

102 Stuart, G.J. and Sakmann, B. (1994) Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. *Nature* 367, 69–72

103 Häusser, M. *et al.* (1995) Axonal initiation and active dendritic propagation of action potentials in substantia nigra neurons. *Neuron* 15, 637–647

104 Kaiser, K.M.M. *et al.* (2001) Back-propagating action potentials mediate calcium signalling in dendrites of bitufted interneurons in layer 2/3 of rat somatosensory cortex. *J. Physiol.* 535, 17–31

105 Traub, R.D. and Miles, R. (1995) Pyramidal cell-to-inhibitory cell spike transduction explicable by active dendritic conductances in inhibitory cell. *J. Comput. Neurosci.* 2, 291–298

106 Goldberg, J.H. *et al.* (2003) $Ca^{2+}$ imaging of mouse neocortical interneurone dendrites: Ia-type $K^+$ channels control action potential backpropagation. *J. Physiol.* 551, 49–65

107 Cook, E.P. and Johnston, D. (1997) Active dendrites reduce location-dependent variability of synaptic input trains. *J. Neurophysiol.* 78, 2116–2128

108 Perez, Y. *et al.* (2001) A hebbian form of long-term potentiation dependent on mGluR1a in hippocampal inhibitory interneurons. *Proc. Natl. Acad. Sci. U. S. A.* 98, 9401–9406

109 Alle, H. *et al.* (2001) PTP and LTP at a hippocampal mossy fiber–interneuron synapse. *Proc. Natl. Acad. Sci. U. S. A.* 98, 14708–14713

110 Zilberter, Y. *et al.* (1999) Dendritic GABA release depresses excitatory transmission between layer 2/3 pyramidal and bitufted neurons in rat neocortex. *Neuron* 24, 979–988

111 Kraushaar, U. and Jonas, P. (2000) Efficacy and stability of quantal GABA release at a hippocampal interneuron–principal neuron synapse. *J. Neurosci.* 20, 5594–5607

112 Forti, L. *et al.* (2000) Action potential-evoked $Ca^{2+}$ signals and calcium channels in axons of developing rat cerebellar interneurones. *J. Physiol.* 527, 33–48

113 Southan, A.P. *et al.* (2000) Hyperpolarization-activated currents in presynaptic terminals of mouse cerebellar basket cells. *J. Physiol.* 526, 91–97

114 Bartos, M. *et al.* (2001) Rapid signaling at inhibitory synapses in a dentate gyrus interneuron network. *J. Neurosci.* 21, 2687–2698

115 Gibson, J.R. *et al.* (1999) Two networks of electrically coupled inhibitory neurons in neocortex. *Nature* 402, 75–79

116 Galarreta, M. and Hestrin, S. (1999) A network of fast-spiking cells in the neocortex connected by electrical synapses. *Nature* 402, 72–75

117 Galarreta, M. and Hestrin, S. (2002) Electrical and chemical synapses among parvalbumin fast-spiking GABAergic interneurons in adult mouse neocortex. *Proc. Natl. Acad. Sci. U. S. A.* 99, 12438–12443

118 Deans, M.R. *et al.* (2001) Synchronous activity of inhibitory networks in neocortex requires electrical synapses containing connexin36. *Neuron* 31, 477–485

119 Hormuzdi, S.G. *et al.* (2001) Impaired electrical signaling disrupts gamma frequency oscillations in connexin 36-deficient mice. *Neuron* 31, 487–495

120 Tamás, G. *et al.* (2000) Proximally targeted GABAergic synapses and gap junctions synchronize cortical interneurons. *Nat. Neurosci.* 3, 366–371

121 Trussell, L.O. (1999) Physiology of glutamatergic transmission at calyceal and endbulb synapses of the central auditory pathway. In *Ionotropic Glutamate Receptors in the CNS. Handbook of Experimental Pharmacology* (Vol. 141) (Jonas, P. and Monyer, H., eds), pp. 399–418, Springer

122 Wang, L-Y. *et al.* (1998) Contribution of the Kv3.1 potassium channel to high-frequency firing in mouse auditory neurones. *J. Physiol.* 509, 183–194

123 Fuchs, E.C. *et al.* (2001) Genetically altered AMPA-type glutamate receptor kinetics in interneurons disrupt long-range synchrony of gamma oscillation. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3571–3576

124 Katona, I. *et al.* (1999) Postsynaptic targets of somatostatin-immunoreactive interneurons in the rat hippocampus. *Neuroscience* 88, 37–55

125 Normann, C. *et al.* (2000) Associative long-term depression in the hippocampus is dependent on postsynaptic N-type $Ca^{2+}$ channels. *J. Neurosci.* 20, 8290–8297