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Neurogliaform Cells in Cortical Circuits

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Abstract

Recent research into local circuit GABAergic inhibitory interneurons of the mammalian central nervous system has provided unprecedented insight into our understanding of the mechanics of neuronal circuitry and its dysfunction. The recognition that inhibitory interneurons represent a broad array of anatomically and neurochemically diverse cell types suggests that each occupy an equally diverse functional role. Although neurogliaform cells were observed by Cajal over a century ago, our understanding of their functional roles is in its infancy. However, it is rapidly becoming clear that this cell type operates under a distinct repertoire of rules to provide novel forms of inhibitory control of numerous afferent pathways.

Although GABAergic local circuit inhibitory interneurons represent only ~20% of the total cortical cell population their anatomical diversity is unparalleled in the mammalian central nervous system; for example there are currently upwards of 20 acknowledged distinct members within the CA1 hippocampal formation alone[1]. Their anatomical diversity is rich, with the morphologies of many cell types remaining local to a particular subfield, while other cell types extend wide arbor dendrites and axons that cross numerous cortical and hippocampal layers and subfields. Inhibitory interneurons often demonstrate exquisite targeting of their axons to differential postsynaptic structures. For example, axons can target selective subcellular domains (e.g. the perisomatic, axon initial segment or specific dendritic domains) to compartmentalize or time electrical activity in either a positive or negative manner. Alternatively, axons can make projections several millimeters in length, to innervate thousands of postsynaptic targets to co-ordinate the activity of both homogeneous and distributed neuronal ensembles[2,3–5]. A comparative newcomer to the interneuron scene is a small distinctive cell that resides primarily within the hippocampal stratum radiatum and lacunosum-moleculare (SLM), and both the superficial and deep layers of the neocortex; commonly referred to as the neurogliaform cell (NGF). The purpose of the present review is to integrate the current literature to highlight the unique properties and roles played by this cell type.

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Distinctive morphology of NGF cells

In 1899 Santiago Ramón y Cajal[6] wrote of a "short axon cell type" observed in 1 month old human motor cortex tissue.

> **"Cells with a Short Axon**
>
> **B) Dwarf or Neurogliaform Cells.** These very small cells with a short axon, which we discovered in the human cerebral cortex are distinguished by a tiny perikaryon, as well as by the thinness and abundance of their radiating dendrites. They are found throughout the cortex, particularly in deeper layers. …… their polygonal cell body issues a great many thin, varicose, very poorly branched, short dendrites from each of its crests. At first glance, these neurons could be mistaken for astrocytes with short processes if it were not for the absence of lateral outgrowths on the dendrites and the presence of an axon. The latter is very thin, to a point of only staining yellow with silver chromate. Shortly after arising it generates a very dense arborization of delicate, moniliform branches that can be examined only with an apochromatic objective. Sometimes only the arborization is impregnated, with the perikaryon and dendrites remaining invisible; this feature enhances its examination."

This cell type, which he identified as existing across many cortical areas, he interchangeably referred to as *dwarf, spiderweb, arachniform or neurogliaform*. Surprisingly, in his subsequent documentation of cells with short axons within the hippocampal formation, Cajal did not describe the NGF cell and it would take several decades before this cell type would be definitively identified in the hippocampus. The seminal publication of Lacaille and Schwartzkroin[7] (see figure 3a of that publication) may provide the first image of a neurogliaform-like cell within the hippocampal CA1 SLM. Subsequent work by the groups of Ben-Ari, Buhl, and Capogna clearly established this cell as a major hippocampal inhibitory interneuron subtype[8–10].

NGF cells represent approximately 10% of the total hippocampal inhibitory interneuron population[3]. NGF cells of both cortex and hippocampus are immunopositive for neuropeptide Y, reelin, α-actinin-2, COUPTFII and nNOS[3, 11–13]. However, with the exception of NPY no single marker labels the entire NGF cell population (almost all NGF cells are NPY-positive but not all NPY-positive cells are NGF cells). Unlike the cortex where all NGF cells are derived from the caudal ganglionic eminence (CGE) [11], NGF cells of the hippocampus have their origins within both the CGE and the medial ganglionic eminence (MGE) [13] (Box 1). MGE-derived NOS+ NGF cells share many features in common with another population of MGE-derived hippocampal NPY+ inhibitory interneurons, the so-called Ivy cells, which reside in all layers of the CA1 hippocampus with the exception of the SLM[12, 14, 15]. Ivy cells represent the largest single population of hippocampal inhibitory interneuron (23% of total inhibitory interneurons)[3], and like many NGF cells are both NPY +, COUPTFII+ and nNOS+ but unlike NGF cells do not express reelin. Whether the neocortex harbors a similar Ivy cell population remains an open question. Finally, NPY-*negative* NGF-cells have been reported in both cortical layer I (termed the *elongated* NGF cell)[16] and striatum[17] raising the possibility that there exists a third NGF cell type that has

not been previously included in any classification schemes or whose origins have been identified through genetic approaches.

Box 1

Developmental Origins of NGF cells

Inhibitory interneurons of the neocortex and hippocampal formations are generated in the neurogenic medial and caudal ganglionic eminences (MGE and CGE respectively) of the ventral telencephalon[86–88]. Although the cortex and hippocampal structures share many of the same rules for interneuron embryogenesis a number of notable exceptions exist[13, 14, 89, 90].

The vast majority of neocortical NGFs are reelin-, NPY- and COUPTFII-positive with only a small percentage positive for nNOS[11]. Neocortical NGF cells have their origins within the CGE[91]. The initiation and peak production of neocortical NGF cells occurs at E12.5 and E16.5 respectively[1191]. In contrast hippocampal NGF cells arise from both the MGE and CGE. Like their neocortical counterparts, NOS-negative NGF cells arise exclusively from the CGE[13, 14] between E12.5 and E16.5. In contrast, the vast majority of nNOS-positive NGF cells arise from the MGE, with only a small number of nNOS+ NGF cells originating from the CGE[13, 91]. MGE-derived hippocampal nNOS+ NGF cells are generated earlier than their CGE counterparts, between E9.5 and E13.5; with the majority of nNOS+ cells (>50%) being generated at ~E13.5.

Neurochemically heterogeneous NGF cells with distinct embryonic and temporal origins suggests a duplication of the NGF cell occurred during evolution, which has given rise to anatomically and functionally similar cell types that either contain or lack nNOS. The observation that cortical and hippocampal CGE-derived NGF cells are nNOS-negative and that both are born and migrate with similar time frames to superficial layers of each structure (the SLM is essentially the layer 1–2 of the hippocampus) suggest that these cells represent a single population of NGF cells. MGE-derived nNOS-positive NGF cells are generated earlier and provide a second distinct population, which tend to migrate to the deeper SLM and are more often found are the border between the SLM and St. radiatum [13] (Figure 1). The presence or absence of nNOS may endow each cell type with a distinct role in spatially coordinating hippocampal haemodynamics with changes in local network activity[1352, 92]. Furthermore nNOS can act as a retrograde transmitter suggesting that nNOS containing NGF cells may have a select role in regulating activity in its pre- and postsynaptic partners[53].

In the CA1 subfield the somata of NGF cells are confined largely to the SLM, with a smaller distinct population of cells located at the border of SLM that penetrate stratum radiatum (~15% of total NGF cells)[10, 13]. In CA1 NGF cells possess a small spherical soma of ~10–20mm in diameter. Their dendrites branch repeatedly to form a small dense stellate plexus around the somata, which are often contained within the axon cloud (Figure 1). The dense axonal arborization of NGF cells, which can originate from either the soma or dendritic compartment[18, 19] typically remains close to the somato-dendritic profile (Figure 1, Figure 2a). Peter Somogyi and colleagues[20] observed that the axonal expansion of a single CA1

SLM NGF was ~ 500 μm in the mediolateral axis and 1200 μm in the septotemporal axis. The axonal arborization has been calculated to approximate 140,000 μm in length[3] compared to ~46,000 μm for a typical parvalbumin basket cell[21]. The axons of CA1 NGF cells can cross the fissure and penetrate the dentate gyrus[20]. Similarly, axons of NGF cells within the stratum moleculare of the dentate gyrus can penetrate the fissure and cross into the CA1 subfield[18]. This cross subfield axonal arborization may serve to functionally link the dentate gyrus and CA1. Recent evidence suggests that the ultimate spatial position of migrating cortical NGF cells as well as the elaboration of it axonal arborization is controlled both by the cells intrinsic neuronal activity as well as appropriate inputs from specific afferent projections [2223].

Despite occupying a relatively small volume the presynaptic bouton density of NGF cells is amongst the highest of all hippocampal interneurons with the average bouton density close to 42 per 100 μm of axon (interbouton separation 2.5 μm)[3]. For comparison, parvalbumin basket cells and somatostatin-positive OLM cells each have an average bouton density of ~23/100 μm^3. Olah et al (2009)[24] observed that the density of boutons on a single NGF matched the release site density of 5–6 overlapping basket cell axons. ~92% of hippocampal NGF cell synapses are apposed to pyramidal neurons with the remainder being made onto other inhibitory interneurons and Cajal Retzius cells of the SLM[3, 25]. One feature of NGF cells that separates them from all other inhibitory interneurons is the observation that the vast majority of synaptic boutons are spatially located at a larger than usual distance from their target dendrites. In somatosensory cortex the separation between NGF axons and the dendrite targets was calculated to be 2.7μm (range 1.1 – 5.0 μm)[24]. This observation coupled with their dense bouton arrangement has led to the widespread belief that NGF cells are not involved primarily with “point to point” synaptic transmission but release GABA in a target independent, volume- or “cloud-like”- manner to generate a non specific form of inhibitory control (see below).

Intrinsic Physiology of NGF Cells

The intrinsic firing properties of NGF cells differ in many respects from other inhibitory interneuron types and are likely tuned to reflect the unique roles played by these cells in the circuits in which they are embedded. CA1 hippocampal NGF cells possess resting membrane potentials close to −60mV, have relatively low input resistances and fast membrane time constants[13]. A hallmark feature of NGF cells is a delay to generate action potentials when challenged by a just suprathreshold current injection (Figure 2b)[26]. This “late spiking” phenotype[27] is consistent between nNOS-containing and nNOS-lacking NGF cells. In fact a comparison of numerous intrinsic properties of CA1 nNOS-containing versus nNOS-lacking NGFs revealed no differences between the two cell types[13] (Figure 2a,b). This late spiking activity may allow the NGF cell to act as a slow integrator of changes in either membrane potential or incoming activity across many 10s of milliseconds prior to its output of action potential activity.

Action potential amplitude is relatively small, duration is moderate and typically followed by a brief, but large after hyperpolarization (Figure 2b)[13]. Their firing patterns are largely non-accommodating and often accelerate as the depolarizing pulse proceeds. Of interest,

NGF cells of the dentate gyrus molecular layer have more negative resting membrane potentials[18]. The physiological consequences of this are at present unclear, but negative resting potentials are also a hallmark feature of granule cells (GC), the principal neuron of the dentate gyrus, suggesting a homeostatic balance in regional excitability may exist.

Cells that possess a late spiking phenotype typically demonstrate a slow depolarizing ramping of their just subthreshold voltage trajectory (Figure 2b). This slow depolarization likely indicates an intrinsic voltage conductance with either time dependent activation or inactivation. Although no study to date has characterized voltage gated conductances in targeted NGF cells, interneurons of the SLM possess a complement of outward voltage-gated K^+ conductances distinct from other hippocampal inhibitory interneurons[28–31]. These interneurons lack a prominent transient A-type current and possess a rapidly activating and slowly inactivating “delayed rectifier” current likely formed by Kv3.2[32, 33].

NGF cells of several cortical and hippocampal regions possess a novel action potential firing profile known as *persistent* or *retroaxonal barrage* firing[34–37] (Figure 2c). Barrage firing represents a novel form of slow integration that is triggered in response to prolonged action potential activity. This persistent firing is generated within the axon compartment by an as yet unidentified mechanism and once generated can persist for several minutes after the trigger has elapsed. Once initiated NGF cells fire at frequencies ranging from 20 – 130Hz depending on the particular region under study[37]. Persistent firing is not blocked by antagonists of $GABA_A$ and $GABA_B$, AMPA or NMDA receptors[34] but its induction can be inhibited (at least in hippocampal NPY-positive Ivy cells) by activation of μ-opioid peptide receptors[36], which act to either hyperpolarize the NGF or to inhibit the locally gap junction connected NGF network. Importantly, persistent firing, which likely represents a mechanism to provide a global “brake” on local excitability, occurs in NGF cells both *in vitro* and *in vivo* although it appears to occur with less frequency in the latter and to require a more prolonged barrage of action potential activity for its initiation in neocortical NGF cells *in vivo*[37]. As discussed below the inhibitory synaptic output of NGF cells rapidly declines during sustained trains of presynaptic activity, therefore its unclear exactly how much inhibition is being provided to postsynaptic targets during NGF cell barrage firing.

Afferent input onto NGF cells

A quantitative assessment of CA1 local circuitry has calculated that inhibitory interneurons within the CA1 subfield receive ~ 5–10% of all available glutamatergic synaptic inputs[38]. Based on these observations a “hypothetical” interneuron of the CA1 subfield would typically receive between ~8000–17000 Schaffer collateral inputs and an additional 1300 entorhinal inputs[3] with the ratios of these inputs largely dictated by the anatomical location of the cell’s soma and dendrites.

The position of NGF cells within the CA1 hippocampal SLM largely overlaps with glutamatergic afferents arriving from the entorhinal cortex and thalamus, and suggests that they probably receive minimal Schaffer collateral input from the CA3 subfield. However, the small population of NGF cells with cell bodies close to the SLM-radiatum border and whose dendrites extend into stratum radiatum likely receive additional excitatory input via Schaffer

collateral inputs. Although NGF cells receive glutamatergic synaptic input via both AMPA- and NMDA-preferring receptors[8, 18], surprisingly little is known about the biophysical properties of these inputs. In early recordings NGF cells of the CA1 subfield were shown to receive excitatory input from both entorhinal- and Schaffer collateral inputs[8] that demonstrated either short-term depression of synaptic transmission or initial facilitation followed by depression of transmission[8]. NGF cells of the dentate gyrus molecular layer receive AMPA receptor mediated excitatory input via the perforant path that shows paired pulse facilitation. Although evidence points to NGF cells expressing both AMPA and NMDA receptor synaptic receptors, no information exists about the relative contributions of these receptors. Schaffer collateral inputs onto the closely related MGE-derived NPY-positive, Ivy cell reveals an AMPA:NMDA ratio of ~5:1[39]. NMDA receptor mediated synaptic currents are a minor conductance on these and other MGE-derived inhibitory interneurons compared to Schaffer collateral inputs onto CGE-derived interneurons. Whether this MGE-versus CGE-dependent segregation of AMPA:NMDA ratios is also mirrored in entorhinal inputs onto different NGF cells remains to be determined.

One intriguing aspect of excitatory input onto NGF cells was recently demonstrated by Quattrocolo and Maccaferri (2014)[40] who revealed a monosynaptic glutamatergic input onto NGF cells originating from Cajal-Retzius cells located within the CA1 SLM. Optogenetically driven glutamate release from Cajal-Retzius cells activated both AMPA- and NMDA-receptor mediated synaptic currents in NGF cells. The functional role of this connection is at present unclear but given the essential role for Cajal-Retzius cells in cellular and dendritic development one could speculate that this connection has a role in structural and functional development and plasticity of NGF cells.

Early studies demonstrated that stimulation of almost all hippocampal CA1 subfields could trigger monosynaptic $GABA_A$ and $GABA_B$ receptor mediated inhibitory input onto NGFs[9, 41]. Paired pulse stimulation revealed these inhibitory inputs to possess relatively slow time constants of decay (~40msec) and to be largely depressing in nature. Paired recordings between hippocampal NGF cells revealed that the vast majority of cells were coupled through both electrical and chemical synapses[8]. Recordings in human and rodents also revealed that cortical NGF cells receive monosynaptic $GABA_A$ and $GABA_B$ receptor mediated inhibitory input from other NGF cells[42]. These monosynaptic events were longer lasting; rise times and half widths were ~6msec and 45msec respectively. Blockade of $GABA_B$ receptors reduced the response half width by ~20% underscoring a role for both $GABA_A$ and $GABA_B$ receptors. The observation that hippocampal NGF cells possess spontaneous inhibitory postsynaptic currents (IPSCs) with a variety of time courses suggested that other sources of inhibitory input onto NGF cells must also exist[43].

Output of NGF cells

There are two well established modes of $GABA_A$R-mediated inhibition with phasic (or synaptic) signaling referring to conventional point-to-point transmission whereas tonic signaling results from activation of receptors by ambient GABA in the extracellular space. The spatiotemporal concentration profiles of transmitter mediating these two signaling processes have distinct consequences for receptor-mediated currents, with the high and brief

GABA transient in the synaptic cleft (> 1 mM for < 0.5 ms) driving rapid receptor activation and deactivation, while persistent low concentrations of GABA favors a gradual equilibration of receptors between desensitized and open states[44] (Figure 3a and b) Interestingly, NGF cells mediate a third form of GABAergic transmission intermediate between phasic and tonic signaling, which in CA1 has been referred to as $GABA_{A,slow}$[26]. In contrast to the rapid IPSCs produced at typical synapses made by perisomatic-projecting interneurons such as basket cells, NGF cells generate slower IPSCs that result from prolonged GABA transients with a low peak concentration[43, 45, 46]. The unusual GABA concentration transient likely results from the densely spaced NGF cell presynaptic terminals, some without postsynaptic specializations, that allow GABA to reach both synaptic and non-synaptic receptors located at a distance from release sites, in a form of volume transmission[24] (Figure 3c). Thus synaptic currents evoked by NGF cells exhibit hallmarks of spillover signaling that reflect the action of GABA outside the synapse [43, 46, 47].

What are the functional consequences of volume transmission from NGF cells? First, the low and prolonged GABA transient favors postsynaptic receptor desensitization, resulting in use-dependent synaptic depression as receptors accumulate in desensitized states[43]. Second, in contrast to other interneuron subtypes that precisely target distinct subcellular domains, inhibition mediated by NGF cells generally lacks target cell and synaptic specificity. That is, the cloud of GABA released from NGF cells can act on $GABA_A$ receptors located on any nearby neuronal element, including the releasing cell itself, potentially producing suppression of neural activity in a widespread area dictated by their dense NGF cell axonal arbor[24, 43] (Figure 3). Third, NGF cells provide a major source of slow $GABA_B$ receptor-mediated inhibition. Whereas other interneuron subtypes require high frequency stimulation to engage pre- and postsynaptic $GABA_B$ receptors that are typically located outside the synapse[48, 49], single action potentials in NGF cells can activate postsynaptic $GABA_B$ receptor-mediated inhibition as well as presynaptic $GABA_B$ receptors that mediate homosynaptic and heterosynaptic depression[8, 18, 24, 42, 50]. These characteristics of synaptic signaling sharply contrast with transmission from other interneuron subtypes that exhibit strong temporal and spatial selectivity. The unexpected specificity of presynaptic $GABA_B$ receptor activation by NGF cells in the barrel cortex[51] however highlights the need for additional understanding of synaptic transmission mediated by NGF cells and its role in network activity that appears more complex than expected.

An additional topic ripe for exploration is the role of other neuroactive peptides, such as NPY, reelin, nNOS and insulin, in NGF cell function. Notably, NGF cells and Ivy cells comprise a major fraction of nNOS-expressing interneurons and NOS is a well-known retrograde modulator of synaptic transmission as well as a mediator of neurovascular coupling[1952]. Physiologically-relevant firing patterns induces release of NO from NGF cells that inhibits GABA release from impinging NGF cell terminals, in a form of retrograde signaling reminiscent of depolarization-induced suppression of inhibition (DSI) mediated by endocannabinoids[53]. NO release is induced by back propagating action potentials that trigger L-type Ca^{2+} transients in NGF cell dendrites and the resultant suppression of inhibition is sufficient to transiently enhance excitatory integration of EPSPs. NGF cells in the cortex are also a major source of insulin. Insulin released by NGF cells in response to

locally applied glucose can mimic the effects on synaptic activity induced by bath applied insulin, suggesting that NGF cells might contribute to endogenous insulin signaling[54]. In contrast to NO release, however, insulin does not appear to be released by NGF cell spiking. A greater understanding of the signaling mechanisms mediated by NGF cells is needed to realize their specific roles in network activity.

NGF cells, network activity and oscillations

In CA1 SLM apical tufts of CA1 pyramidal cells are innervated by perforant path afferents that originate in layer III of the entorhinal cortex (also called the temporoammonic pathway; TA). The long electrotonic distance to the soma means that TA inputs are relatively weak but can generate dendritic spikes that drive CA1 spiking when facilitated by Schaffer collateral inputs[55]. Localization in the SLM predicts that NGF cells provide feed-forward inhibition that restricts the time window for integration of TA inputs as well as suppresses TA-induced dendritic spiking (Figure 4). Desensitization of postsynaptic $GABA_A$ receptors during repetitive stimuli, in concert with prominent presynaptic $GABA_B$-mediated and NO-induced auto-inhibition of GABA release, results in an activity-dependent suppression of NGF feed-forward inhibition[43, 5053]. Together these mechanisms for dynamic suppression of dendritic feedforward inhibition, which are prominent at theta frequency (4–10Hz), are likely to enhance integration of TA excitatory inputs. Interestingly, the lack of $GABA_B$ receptors at TA terminals will provide a measure of synapse specificity of spillover-mediated suppression of GABA (but not glutamate) release[50, 56]. Alternatively, CGE-derived NGF cells (but not MGE-derived NGF cells) express the serotonergic ionotropic 5HT3a receptor[57, 58], and likely receive excitatory input from serotonin fibers originating in the Raphe Nucleus. Activation of 5HT3a receptors on nNOS-negative NGF cells may trigger a widespread inhibition of the distal dendrites of CA1 pyramidal cells to shunt activity arriving via the temporoammonic pathway of the entorhinal cortex. This localized inhibition may serve to allow preferential activation of CA1 pyramidal cells via their Schaffer collateral inputs from CA3 (Figure 4). However this scenario is likely an oversimplification as serotonergic raphe fibers also release glutamate and innervate other interneurons[59], potentially leading to more complex outcomes that require further investigation.

Another example of functional specificity of presynaptic inhibition mediated by NGF cells is evident in the somatosensory cortex, where temporal precision of sensory responses in layer IV is maintained by strong thalamic recruitment of feedforward inhibition from PV^+ interneurons. This feed-forward inhibition is suppressed by layer IV NGF cells that generate spillover-mediated activation of $GABA_B$ receptors on PV^+ terminals[51], in a typical example of presynaptic silencing by NGF volume transmission[24, 50]. Despite expression of functional $GABA_B$ receptors on thalamic axon terminals, however, GABA release from NGF cells does not affect thalamic glutamate release[51]. This specificity of $GABA_B$ mediated presynaptic inhibition is surprising, since heterosynaptic depression of glutamate release from cortical terminals provided important evidence for the spatially nonselective nature of NGF volume transmission[24]. Results from the barrel cortex[51] suggest that mechanisms to promote synaptic or spatial specificity of signaling by NGF cells could endow them with unexpected roles in fine-tuning circuit function. Specificity of glutamatergic and cholinergic input to

NGF cells in the somatosensory cortex is also likely to refine their involvement in circuit functions [6061].

NGF cells form prolific chemical and electrical synapses with other interneuron subtypes, suggesting that regulation of inhibitory circuits may be an important circuit function. Unlike most interneuron subtypes that are electrically coupled primarily with other cells of the same subtype, heterologous coupling with distinct interneuron subtypes suggests that NGF cells are poised to monitor network activity by non-synaptic communication [6263]. Interestingly, Maccaferri and colleagues showed that synaptic GABAergic potentials can also propagate via gap junctions between interneurons, including NGF cells, in SLM [64]. Propagation of depolarizing GABA potentials via gap junctions contributed to oscillatory network activity generated by the potassium channel blocker 4-AP, suggesting a combination of synaptic and electrical signaling provides a mechanism for synchronizing interneuron networks containing NGF cells.

Work by Pearce and colleagues suggested that purely synaptic interactions between hippocampal interneurons that generate slow IPSCs (termed $GABA_{A,slow}$) and interneurons that generate IPSCs with fast rise and decay phases (termed $GABA_{A,fast}$) could contribute to oscillatory activity. Initial studies determined that these two kinetic classes of IPSCs were mediated by distinct interneuron subtypes, with $GABA_{A,slow}$ arising from NGF cells[26]. In slice preparations, most spontaneous IPSCs reflect activity of $GABA_{A,fast}$ interneurons, such as perisomatic projecting basket and axo-axonic cells. Banks et al., (2000)[65] showed that activation of $GABA_{A,slow}$ suppresses the rate and amplitude of spontaneous IPSCs in CA1 pyramidal cells for hundreds of milliseconds. Thus NGF cells are poised to regulate the firing patterns of other interneurons. Interestingly, $GABA_{A,slow}$-induced suppression of $GABA_{A,fast}$ recovered with a time constant in the theta frequency, leading these authors to postulate that $GABA_{A,slow}$ provides an intrinsic hippocampal mechanism for theta-frequency modulation of gamma oscillations[66].

Networks of inhibitory interneurons generate oscillations that provide temporal and spatial organization of principal cell activity[4]. Local circuits of connected interneurons with strong and fast synaptic connections, like PV^+ fast-spiking cells, are thought to generate the gamma-frequency oscillations exhibited in many brain regions[67], however, the source and mechanisms underlying theta oscillations has been debated. In hippocampus, theta modulation of perforant path EPSCs *in vivo* supports the idea that theta activity is mainly relayed from the cortex via excitation from the entorhinal cortex[68]. Consistent with this idea, theta oscillations are strongest in the TA termination zone in the SLM. But, the ability to generate theta oscillations under various pharmacological conditions in isolated brain slices has also pointed to the existence of intrinsic mechanisms. White et al, (2000)[66] used network modeling to suggest that interactions between networks of $GABA_{A,slow}$ and $GABA_{A,fast}$ interneurons were sufficient to generate mixed gamma and theta rhythms, an idea also supported by the striking dependence of theta on functional inhibition of PV^+ interneurons[69]. Since NGF cells are a major source of IPSCs with slow kinetics, these results suggest that they could contribute to theta rhythms as well as theta frequency modulation of gamma oscillations via synaptic interactions with other interneuron

subtypes[26, 70]. However, additional studies are needed to understand the specific contribution of NGF cells to oscillatory behavior in isolated and intact preparations.

Activity patterns recorded *in vivo* during exploratory behavior suggest how complex interactions between interneurons, cortical and septal inputs and modulators generate the temporal organization of hippocampal neuronal activity during theta oscillations[70]. In vivo, NGFs and the related Ivy cells are slow-spiking interneurons with broad action potentials. NGFs fire at low frequency during the peak of theta whereas Ivy cells fire at the trough of each oscillation, consistent with afferent input arising from the TA and Schaffer collaterals, respectively[12, 20]. Whereas PV^+ interneurons dynamically modulate firing patterns during movement, sleep and transitions between behavioral states, Ivy/NGFs maintain similar low rates and patterns across behavioral states and oscillatory patterns, suggesting highly distinct roles in structuring network activity[71].

Less is known about the role of interneuron subtypes in the activity patterns of the dentate gyrus, mainly due to the relative paucity of in vivo recordings from this region that exhibits unusually sparse population coding. Many *in vitro* and modeling studies have indicated, however, that the dentate gyrus exhibits particularly strong inhibitory circuitry that is important for maintaining activation of only small subsets of granule cells (GCs). Precisely how NGF cells contribute to sparse dentate GC activation is unclear, but their unique properties suggest NGF cells complement the role of other interneuron subtypes. For example, perforant path afferents preferentially recruit fast-spiking basket cells over GCs due to higher excitatory current densities, triggering strong feed-forward inhibition[72] (Figure 5a). This scenario could be similar for NGFs that receive robust perforant path input across their small somatodendritic domains[18]. Basket cells, however, also receive feedback excitation that promotes frequency-dependent burst firing during repetitive perforant path stimulation[72, 73] whereas NGF cells in the molecular layer are unlikely to participate in feedback inhibition. Furthermore, prolific chemical and electrical synapses with other interneuron subtypes, as well as the ability to generate $GABA_B$-mediated inhibition, suggest NGF cells have complex interactions that contribute to network functions[18]. In fact, stimulation in the molecular layer generates slow inhibition of perisomatic-projecting interneurons and prolonged suppression of spontaneous IPSCs in mature GCs[47] (Figure 5b), similar to the interactions between $GABA_{A,slow}$ and $GABA_{A,fast}$ circuits previously described in CA1[65]. Thus NGF cells across hippocampal subregions may have similar network functions.

A role for NGF cells in adult born neuron circuit integration

High levels of intracellular chloride in progenitor cells and immature neurons leads to $GABA_A$ receptor-mediated depolarization, enabling GABAergic activity to trigger Ca^{2+}-dependent signaling cascades essential for proliferation, survival and growth. GABAergic signaling therefore has trophic functions in the embryonic brain as well as in adult neurogenic regions[74, 75]. The early appearance of NGF cells in developing cortical circuits and their target-independent mechanism of signaling makes NGF cells attractive candidates for providing trophic GABA signaling to developing principal neurons. Other signaling

factors expressed by NGF cells including reelin, NOS and NPY are also known to participate in circuit formation.

The role of GABA mediated depolarization in neural maturation has been studied extensively in the context of hippocampal adult neurogenesis, where resident stem cells continually produce new dentate GCs that integrate into the preexisting circuit and acquire mature physiological characteristics over the course of many weeks. Pivotal early studies showed that impairing GABA mediated depolarization by knocking down the sodium-potassium-chloride exchanger NKCC1 that maintains a high intracellular [Cl^-] in immature neurons dramatically impairs subsequent maturation and survival[76, 77]. The robust consequences of manipulating GABAergic signaling on adult neurogenesis raised the question of whether specific interneuron subtypes have preferential control over neural development [75]. This idea was suggested by infrequent GABAergic postsynaptic currents with slow rise and decay phases in newborn neurons, whereas mature neurons display numerous IPSCs with heterogeneous fast and slow kinetics[78, 79]. Markwardt et al, (2009)[80] showed that GABAergic postsynaptic currents in new adult born neurons exhibited characteristics of signaling from NGF cells, including high sensitivity to blockade of GABA transporters and to low affinity $GABA_A$ receptor antagonists. Innervation by NGF cells is also consistent with slow spontaneous synaptic currents in newborn GCs that are correlated with slow, but not fast, sIPSCs in simultaneous recordings of neighboring mature GCs (Figure 5c)[80]. Yet evoking synaptic currents using focal stimulation made it difficult to unambiguously differentiate signaling from NGF cells from non-specific GABA spillover from nearby basket cell terminals, hence, subsequent paired recordings confirmed that stimulation of single NGF is sufficient to generate slow GABA postsynaptic currents in newborn GCs[47]. These results suggest a local circuit in which newborn GCs are initially responsive primarily to GABA release from NGF cells with subsequent innervation from other interneurons developing during the course of maturation[75].

GABAergic signaling by NGF cells constitutes a form of volume transmission that potentially activates perisynaptic or extrasynaptic $GABA^A$ and $GABA^B$ receptors, both of which have been implicated in regulation of progenitor proliferation prior to synapse formation[75, 81]. This form of transmission may be optimized for trophic signaling to cells in a dynamic period of dendrite motility and outgrowth prior to synapse stabilization, in a mechanism of signaling that could also be accomplished by spillover from densely packed conventional synapses for other interneuron subtypes[82, 83]. In addition to promoting depolarization-induced Ca^{2+} influx needed for regulation of proliferation and growth, Chancey et al (2013)[84] demonstrated that GABAergic depolarization directly contributes to excitatory synaptogenesis of adult born neurons. Newborn neurons at an early stage of maturation have glutamatergic transmission mediated solely by NMDAR-only containing (silent) synapses that incorporate AMPA receptors in response to neural activity. Both NMDAR activation and GABA-mediated depolarization that allows relief from voltage-dependent block of NMDARs is required for this initial synapse unsilencing[84]. Hence there is a need for coordinated GABA and glutamate-mediated transmission. Initial silent synapses on adult born neurons arise from glutamatergic hilar mossy cells that comprise the associational/commissural pathway. Selective optogenetic activation of hilar mossy cell axons generates not only NMDAR EPSCs, but also di-synaptic depolarizing GABA

currents[85]. Although further studies are required to determine whether di-synaptic GABA release arises from NGF cells, the slow time course comparable to NMDAR EPSCs supports that possibility. Together these results suggest that NGF cells contribute to activity-dependent regulation of neuronal maturation as well as early synaptogenesis during circuit assembly.

Conclusions

Once a cell type largely unexplored, NGF cells are emerging as an interneuron class capable of governing many diverse processes from circuit development to sculpting the activity of large neuronal ensembles. Their unique anatomy coupled to a hybrid phasic/tonic mode of GABAergic signaling mechanisms endows NGF cells with mechanisms for widespread local inhibition as well as a surprising precision in some cases. The presence of a variety of neuromodulators such as nNOS and reelin also suggest they they can exert a broad influence over their circuits independently from simple traditional GABAergic synaptic mechanisms.

In a recent review of fast spiking parvalbumin (PV) interneurons Peter Jonas and colleagues[5], pointed out that the full court press of 20 years of research into PV cells has shown us that we can “close the gaps between the molecular, cellular, network and behavioral levels…and that these results may form the basis for PV interneurons as therapeutic targets”. That such an armament of information has been amassed regarding the PV basket cell is both a satisfying and rewarding accomplishment for the field. That a similar amount of insight could be obtained for all other inhibitory interneuron subtypes is a truly head spinning but realistic proposition and the advent of modern molecular, genetic, physiological and optogenetic approaches makes this tenable within the next decade. Although we consider it a worthwhile pursuit to apply similar research pressure to all inhibitory interneurons, we particularly feel this to be the case for neurogliaform cells. It is time for the field to turn its attention to this deserving cell type and be drawn into its *spiderweb*.

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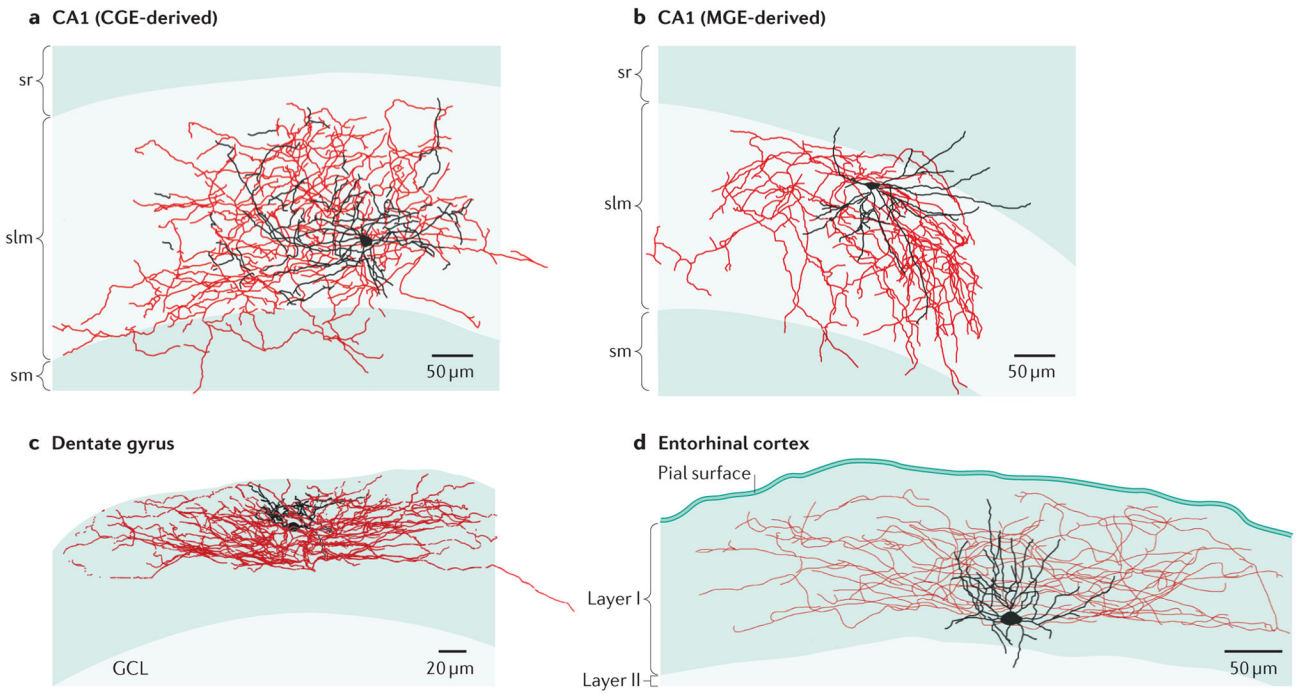

Figure 1.

The diversity of neurogliaform (NGF) cell morphology is exemplified by Neurolucida reconstructions of biocytin recoveries from the hippocampal CA1 medial and caudal ganglionic eminence (MGE- and CGE)-derived NGF cells (parts a and b), dentate gyrus (part c) and entorhinal cortex (part d). Soma and dendrites are shown in black, axons are shown in red. Although the different types of neurogliaform cells illustrate a “stereotypic” anatomy, i.e. small cell body and compact dendrites with dense axonal plexus that stay close to the orbit of the somatodendritic compartment, it is clear that there is marked divergence in their overall anatomical profile that is likely dictated by the network in which they are embedded. CA1 NGFs are taken from Tricoire et al 2010[13]. Dentate gyrus NGF cell used with permission of the authors and taken from Armstrong et al 2011[18]. Entorhinal cortex NGF cell taken from Craig and McBain 2015 [93]

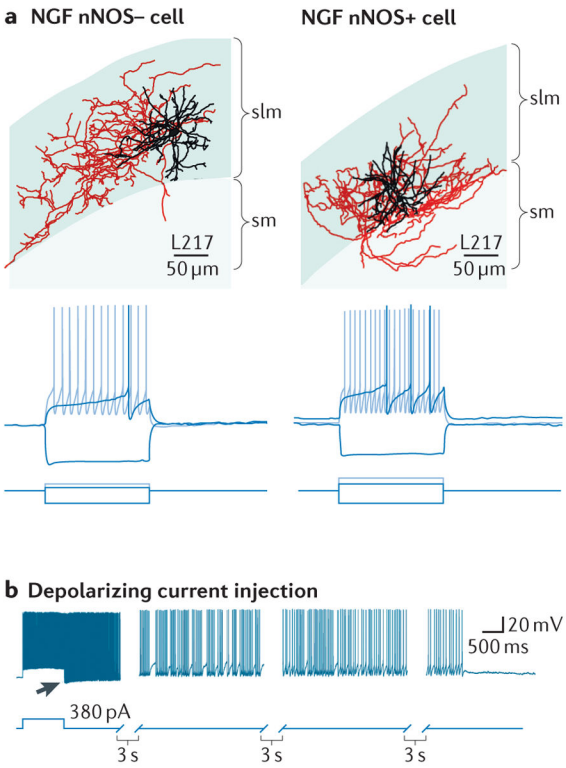

Figure 2.

Anatomical and electrophysiological characterization of neuronal nitric oxide synthase (nNOS)-negative and nNOS-positive CA1 hippocampal NGF cells. A. 'Neurolucida' reconstructions of biocytin filled nNOS-negative and nNOS-positive NGFs cells (soma and dendrites are shown in black, axons are shown in red; scale bar 60µm). Bottom panels show voltage responses of cell types shown in A to three current step injections (hyperpolarizing, just suprathreshold, and twice the current for just suprathreshold). A prominent delay to first action potential is observed in both NGF cell types (black traces). B. NGF cells display persistent firing triggered by repetitive injections of depolarizing current (only the last current step is shown). Persistent firing consists of a period of high frequency spontaneous action potentials (indicated by arrow) that arise from a hyperpolarized membrane potential that gradually diminishes over the course of tens of seconds. Part A taken from Tricoire et al 2010[13]. Part b used with permission of the authors and taken from Krook-Magnuson et al., 2011[36].

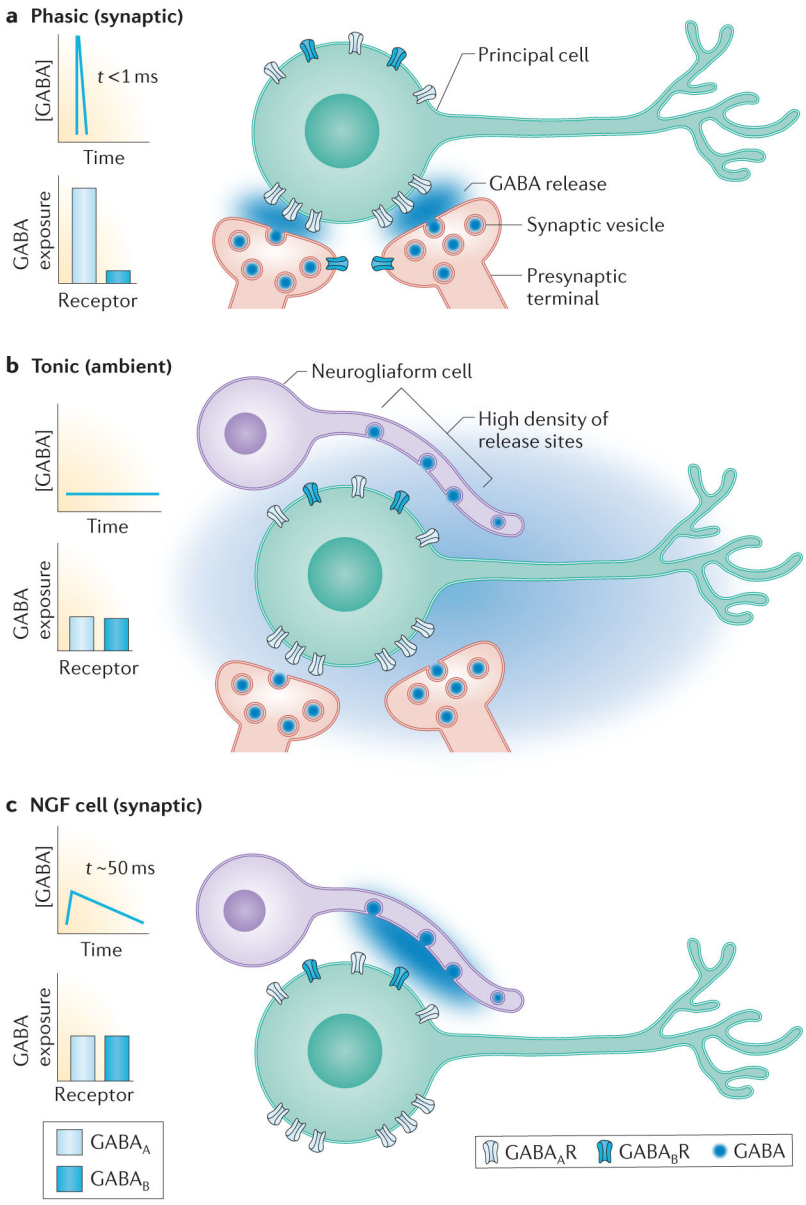

Figure 3.

Distinct forms of signaling generate diverse GABA receptor-mediated responses. The concentration profile of GABA at receptors and the relative likelihood that $GABA_A$ versus $GABA_B$ receptors are exposed to GABA during each mode of transmission is illustrated in the left of each panel A. Phasic or synaptic transmission results from release of GABA-containing vesicles at presynaptic terminals directly opposed to postsynaptic clusters of $GABA_A$ receptors. The small volume of the synaptic cleft and the close proximity of receptors to the release site results in a high concentration of GABA (blue shading) that rapidly declines due to diffusion and GABA transport. $GABA_A$ and $GABA_B$ receptors located outside the synapse are exposed to GABA only during repetitive stimulation or when many closely spaced release sites are synchronously active to generate GABA spillover. B. Tonic activation of $GABA_A$ and $GABA_B$ receptors results from ambient GABA (illustrated

by diffuse blue shading) in the extracellular space. The low level of extracellular GABA is set by activity of GABA transporters and can fluctuate based on surrounding synaptic activity (not shown). Presynaptic $GABA_B$ receptors on NGF cells are activated by ambient GABA. C. Synaptic transmission mediated by NGF cells results from release of GABA-containing vesicles from a high density of terminals on NGF cell axons that can release GABA into the extracellular space. Extrasynaptic $GABA_A$ and $GABA_B$ receptors, as well as presynaptic $GABA_B$ receptors, can be exposed to lower concentrations of GABA that persist for tens of milliseconds. This mode of transmission has characteristics of spillover-mediated signaling.

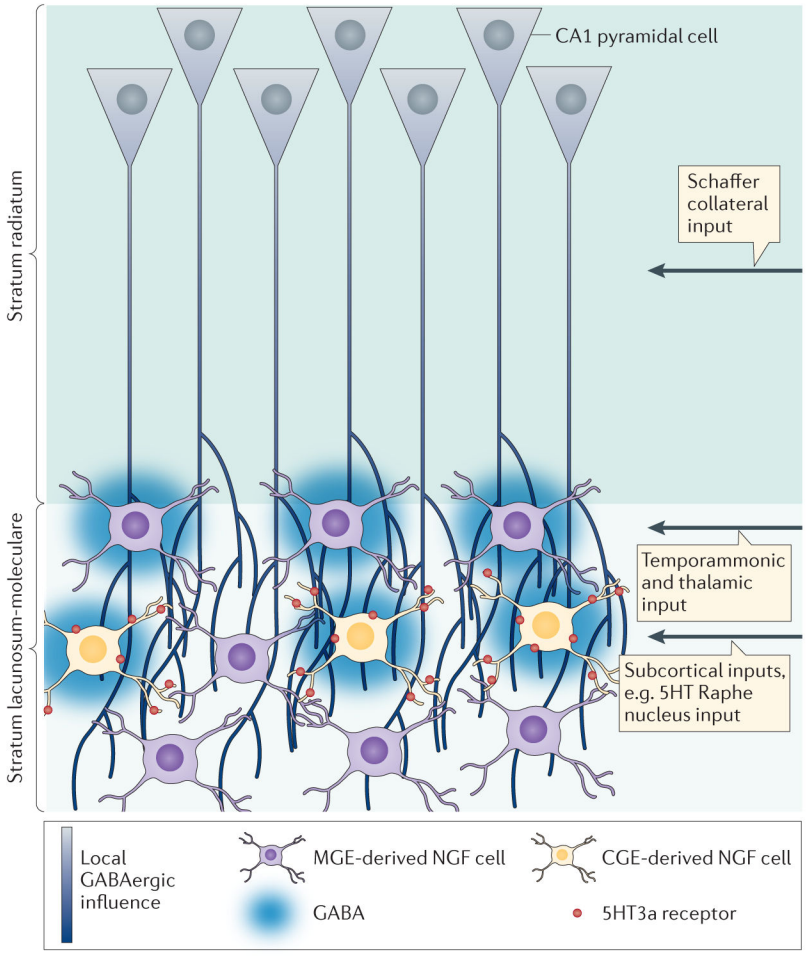

Figure 4.

Two examples of how CA1 Stratum lucidum NGF cells may act as a global gate for afferent information flow. In hippocampus both medial ganglionic eminence (MGE)- and caudal ganglionic eminence (CGE)-derived NGF cells are mainly localized to the stratum lacunosum-moleculare (SLM) or at the SLM-radiatum border. Both cell types act to provide local feed-forward inhibition onto CA1 pyramidal cells (blue) that will modulate the influence of both temporoammonic and thalamic inputs. Alternatively, both MGE-derived NGF cells and CGE-derived NGF cells, which are also rich in ionotropic 5HT3a receptors, may be activated by glutamate and serotonin co-released from subcortical fibers originating in the Raphe Nucleus. Such activation may provide a widespread shunt of activity onto the distal dendrites of CA1 pyramidal cells by virtue of NGF cells inhibitory volume transmission. Shunting excitatory input of temporoammonic inputs will allow input from the CA3 Schaffer collaterals to dominate excitation of CA1 pyramids.

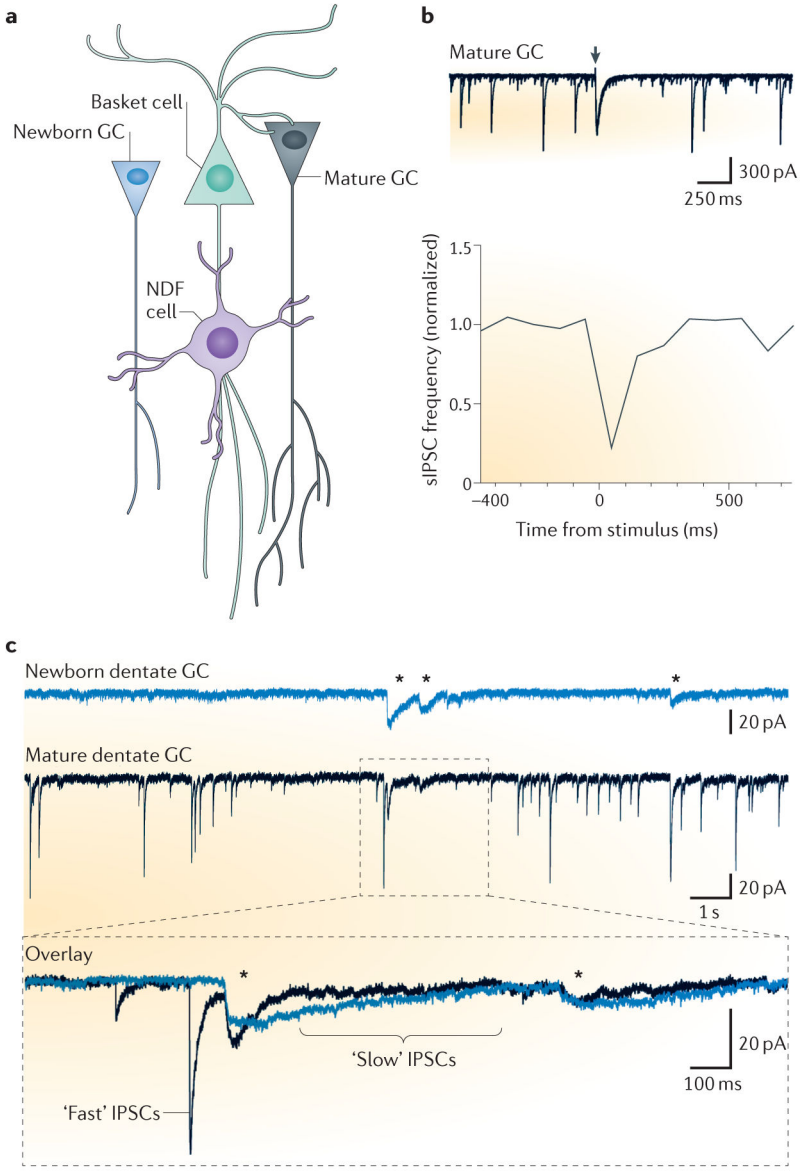

Figure 5.

NGF cells coordinate activity in the neurogenic adult dentate gyrus. A. Schematic diagram showing the synaptic connectivity between NGF cells and dentate granule cells (GCs). GABA released from NGF cell terminals provides inhibition to other interneurons (such as basket cells) and mature GCs, and provides simultaneous depolarization of newborn GCs due to their level of intracellular Cl^-. B, Stimulation in the molecular layer (top panel, arrowhead) generates a slow IPSC in mature GCs (and in basket cells, not shown) that is associated with a reduction in the frequency of fast spontaneous IPSCs recorded in mature GCs (lower panel). This suggests that NGF cells inhibit perisomatic-projecting interneurons like basket cells. C. Simultaneous recordings of spontaneous GABAergic synaptic activity in a newborn dentate GC and neighboring mature dentate GC. Mature GCs exhibit IPSCs with both fast and slow time courses that represent synaptic input from a variety of interneurons whereas newborn GCs exhibit IPSCs with only slow kinetics (asterisks). The expanded view

illustrates that slow IPSCs in the newborn GC showed a high coincidence with slow, but not fast, sIPSCs in the neigbouring mature GC, suggesting that both arise from a common presynaptic interneuron with properties of NGF cells. (Modified with permission from ref [80]).