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TOPICAL REVIEW

Diverse roles for ionotropic glutamate receptors on inhibitory interneurons in developing and adult brain

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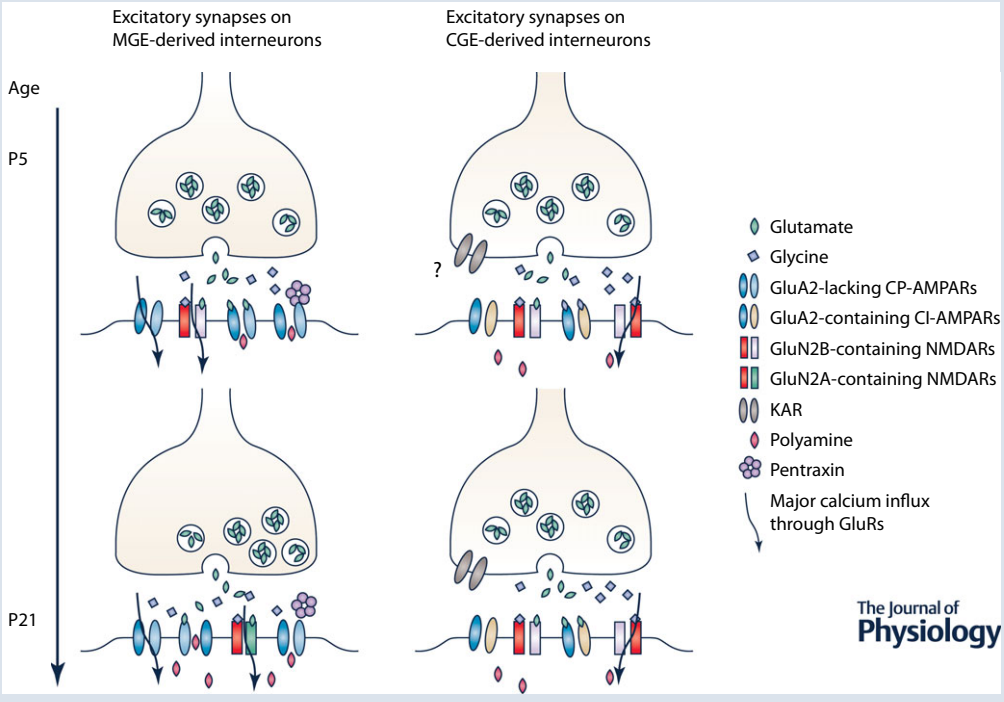

Abstract Glutamate receptor-mediated recruitment of GABAergic inhibitory interneurons is a critical determinant of network processing. Early studies observed that many, but not all, interneuron glutamatergic synapses contain AMPA receptors that are GluA2-subunit lacking and Ca^{2+} permeable, making them distinct from AMPA receptors at most principal cell synapses. Subsequent studies demonstrated considerable alignment of synaptic AMPA and NMDA receptor subunit composition within specific subtypes of interneurons, suggesting that both receptor

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expression profiles are developmentally and functionally linked. Indeed glutamate receptor expression profiles are largely predicted by the embryonic origins of cortical interneurons within the medial and caudal ganglionic eminences of the developing telencephalon. Distinct complements of AMPA and NMDA receptors within different interneuron subpopulations contribute to the differential recruitment of functionally divergent interneuron subtypes by common afferent inputs for appropriate feed-forward and feedback inhibitory drive and network entrainment. In contrast, the lesser-studied kainate receptors, which are often present at both pre- and postsynaptic sites, appear to follow an independent developmental expression profile. Loss of specific ionotropic glutamate receptor (iGluR) subunits during interneuron development has dramatic consequences for both cellular and network function, often precipitating circuit inhibition–excitation imbalances and in some cases lethality. Here we briefly review recent findings highlighting the roles of iGluRs in interneuron development.

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Abstract figure legend Hippocampal and cortical interneurons originate from two different embryonic brain regions, MGE and CGE, and differentiate into multiple subtypes. Recordings from CA1 interneurons targeted by the Schaffer collateral pathway show that, depending on the origin of birth of the postsynaptic inhibitory interneuron type, two distinct glutamatergic synapse types can be observed. Synapses comprising GluA2-lacking, Ca^{2+}-permeable (CP) AMPARs and GluN2A-containing NMDARs (left synapse) are localized on MGE-derived interneurons. On activation by presynaptically released glutamate, AMPA receptors at this synapse type show inwardly rectifying current–voltage relationships due to block of the permeation pathway by intracellular polyamines at more positive voltages. The GluN2A-containing NMDAR contribution at this type of synapse is typically small with AMPA:NMDA ratios often exceeding unity. A second type of synapse comprises GluA2-containing, Ca^{2+}-impermeable (CI) AMPARs, which are resistant to polyamine block and possess essentially linear current–voltage relationships. These synapses have been identified on CGE-derived interneurons. At this synapse, the contribution of GluN2B-containing NMDARs to the synaptic transmission is larger and AMPAR:NMDAR is close to unity.

Abbreviations AMPAR, AMPA receptor; CB, calbindin; CCK, cholecystokinin; CGE, caudal ganglionic eminence of the ventral telencephalon; iGluR, ionotropic glutamate receptor; KAR, kainate receptor; MGE, medial ganglionic eminence of the ventral telencephalon; NMDAR, NMDA receptor; OLM, oriens lacunosum-moleculare; P, postnatal day; PV, parvalbumin; VIP, vasoactive intestinal peptide.

Although comprising only ∼15% of the total cortical and hippocampal neuronal population, inhibitory interneurons provide almost all inhibitory neurotransmission to downstream targets via the neurotransmitter γ-aminobutyric acid (GABA). This extraordinarily diverse neuronal population plays key roles in regulating both local and long-range circuits by forming extensive axonal arborizations with exquisite target selectivity. Interneurons can directly control subthreshold voltage-dependent conductances and regulate both Na^+- and Ca^{2+}-dependent action potential initiation via targeting of GABA release to perisomatic and dendritic compartments (Miles *et al.* 1996). In addition, interneurons have the capacity to entrain the activity of large neural ensembles (Ben-Ari *et al.* 1989; Leinekugel *et al.* 1998; Klausberger *et al.* 2003; Bartos *et al.* 2007; Allen & Monyer, 2015). Historically, cortical and hippocampal interneurons have been classified based on their somatic location, dendritic arborization, axonal targeting, electrophysiological properties, biochemical profiles, and in recent years developmental origins (Freund & Buzsaki, 1996; Cauli *et al.* 1997; Kawaguchi & Kubota, 1997; Monyer & Markram, 2004; Petilla Interneuron Nomenclature *et al.* 2008; Tricoire *et al.* 2011; Welagen & Anderson, 2011). These features when used together can help identify and define the divergent roles of the myriad subtypes of inhibitory interneurons. More recently the advent of genetic approaches and emergence of numerous transgenic mouse lines, which label interneuron subtypes, has accelerated interneuron research (i.e. Figs 1*A* and *B*, and 3*A* and *C*) (Taniguchi *et al.* 2011; Madisen *et al.* 2012).

Interneurons pace and control the activity of neural circuits by leveraging excitation with high spatiotemporal precision. To do this, they must 'sense' the ongoing activity of the neuronal ensembles in which they are embedded and respond in a timely fashion. To this end interneurons of the cortex receive synaptic and non-synaptic glutamatergic input from many different sources: locally via principal neurons distributed across different subfields as well as long-range subcortical afferent pathways. Thus,

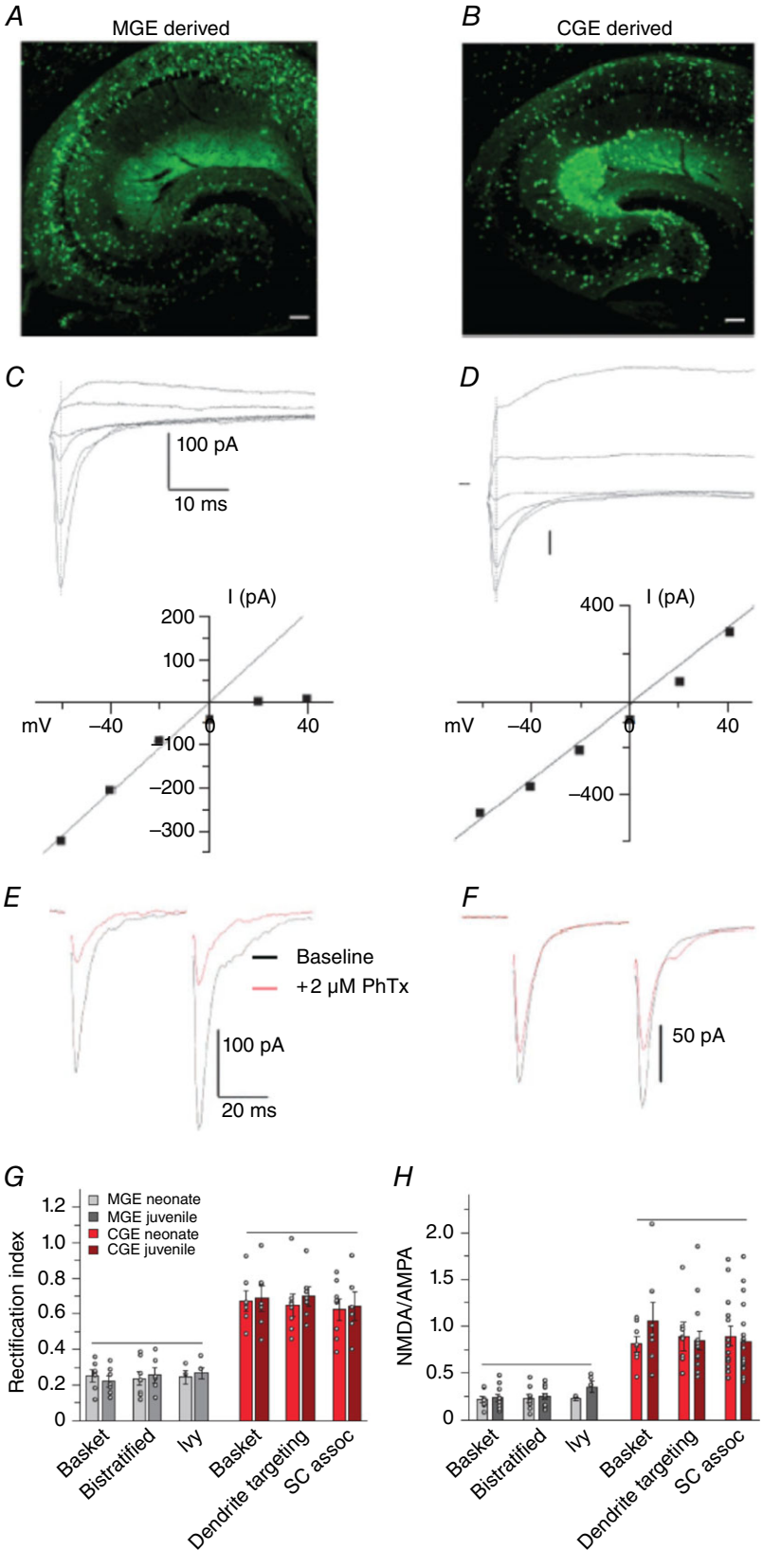

Figure 1. AMPARs on interneuron subtypes show embryonic origin-specific properties
The vast majority of hippocampal interneurons originate from two distinct embryonic regions, the MGE and CGE. MGE- (*A*) and CGE- (*B*) derived cohorts of inhibitory interneurons are shown here labelled with eGFP expression driven by Nkx2.1 or 5ht3ra promoter activity, respectively. *C* and *D*, glutamatergic synapses onto MGE- and CGE-derived interneurons differ in their synaptic properties. Traces are representative of Schaffer collateral-evoked total glutamate receptor (AMPAR and NMDAR)-mediated EPSCs recorded in voltage clamp configuration from MGE-derived (*C*) and CGE-derived (*D*) interneurons of the CA1 stratum radiatum, at holding potentials ranging from −60 mV to +40 mV. The vertical line that crosses the raw traces indicates the time point for the extraction of the AMPAR-mediated fast component of the EPSCs. The plot of these data reveals an inwardly rectifying current–voltage relationship for AMPARs at synapses onto cells derived from the MGE (*C*) and an essentially linear current–voltage relationship for AMPARs onto CGE-derived interneurons (*D*). At positive holding potentials Schaffer collateral–MGE interneuron EPSCs exhibit only a relatively small fast NMDAR component indicating that the contribution of NMDARs at these synapses is low (*C* and *H*). In contrast NMDAR-mediated EPSCs at Schaffer collateral–CGE synapses are relatively large and slow (*D* and *H*). *E* and *F*, AMPARs on MGE- and CGE-derived interneurons show differential sensitivity to block by extracellular polyamines. The traces show AMPAR-mediated EPSCs before (black) and after (red) application of philanthotoxin (PhTx) for representative recordings from MGE-derived (*E*) and CGE-derived (*F*) interneurons. PhTx blocks AMPAR-mediated currents in a use-dependent manner in MGE-derived interneurons to a greater extent compared to CGE-derived interneurons verifying the Ca^{2+}-permeable properties of AMPARs at this synapse. *G* and *H*, graphs summarizing a detailed developmental analysis of the NMDAR- and AMPAR-mediated EPSCs. The current–voltage relationship remains unchanged across two developmental time points (postnatal day P6–9 and P17–21) indicating that the AMPAR subunit composition is not susceptible to developmental regulation (*G*). Across a similar developmental age range NMDA/AMPA receptor ratios are low (~1:5) in three morphologically distinct subtypes of MGE-derived interneurons in CA1 and ~1 in three distinct CGE-derived interneuron subtypes. Reproduced from Matta *et al.* (2013) with permission from the authors.

recruitment of cortical and hippocampal interneurons often depends on the convergence of several excitatory inputs. For example, in the CA1 hippocampus interneurons can potentially receive input from up to five distinct glutamatergic sources, the axons of CA3, CA2 and CA1 pyramidal cells, as well as entorhinal and thalamic afferents, depending on their somato-dendritic position (Miles, 1990; Han *et al.* 1993; Blasco-Ibanez & Freund, 1995; Freund & Buzsaki, 1996; Maccaferri & McBain, 1996; Ceranik *et al.* 1997; McMahon & Kauer, 1997; Vida *et al.* 1998; Chevaleyre & Siegelbaum, 2010). Excitatory inputs onto interneurons are often larger in magnitude than equivalent inputs onto neighbouring principal neurons and in certain interneurons a single excitatory synaptic event is sufficient to trigger action potential firing (Miles, 1990). However, the physiological and pharmacological properties of excitatory input onto different interneuron subtypes is known to vary, giving the first indication of differential receptor subunit expression across different interneuron subtypes (Iino *et al.* 1990, 1996; McBain *et al.* 1992; McBain & Dingledine, 1993; Jonas *et al.* 1994; Isa *et al.* 1996). Until recently little was known concerning the rules and mechanisms regulating the expression of specific iGluR subtypes within particular interneuron subgroups and importantly what the functional significance of receptor variation in a given neuronal network was. In this review we present an overview of some of the differential and unique roles played by iGluRs in both synaptic transmission and circuit integration of interneurons within cortical networks.

Glutamate receptor diversity

Ionotropic glutamate receptors are divided into three subtypes: α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, *N*-methyl-D-aspartate (NMDA) receptors and kainate (KA) receptors. Each receptor subtype comprises distinct subunits that confer specific biophysical properties to the assembled receptors. Expression of several subunits and splice variants of glutamate receptor subtypes have been investigated in different types of neurons in the entire brain and have been extensively reviewed by Traynelis *et al.* (2010).

AMPA receptors

AMPA receptors (AMPARs) are composed of homomers or heteromers (Nakanishi *et al.* 1990; Rosenmund *et al.* 1998) of different combinations of four subunits, GluA1–4 (Keinanen *et al.* 1990). In general, GluA2 subunit-containing AMPARs are Ca^{2+} impermeable whereas the other subunits, in the absence of GluA2, combine to form Ca^{2+}-permeable AMPARs (Hollmann *et al.* 1991; Verdoorn *et al.* 1991). In the hippocampus, initial evidence for AMPA-preferring receptors that differed from the 'traditional' receptors observed on principal cells came from work by Iino and colleagues who demonstrated kainate-induced currents in unidentified cultured cells that exhibited sigmoidal current–voltage (*I–V*) relationships indicative of GluA2-lacking, Ca^{2+}-permeable AMPA receptors (Iino *et al.* 1990; Ozawa *et al.* 1991). McBain & Dingledine (1993) then demonstrated similar inwardly rectifying synaptic AMPARs on CA3 stratum radiatum interneurons. Subsequent reports using *in situ* hybridization and single cell reverse transcription (RT)-PCR combined with electrophysiology showed that in cortical interneurons GluA2 expression is limited, consistent with the presence of inwardly rectifying Ca^{2+}-permeable AMPA receptors (Jonas *et al.* 1994; Geiger *et al.* 1995; Audinat *et al.* 1996). However, the picture was complicated by subsequent reports of GluA2-containing Ca^{2+}-impermeable AMPARs in vasoactive intestinal peptide (VIP)-positive bitufted interneurons (Rozov *et al.* 2001) and calbindin- or parvalbumin- (CB and PV) positive multipolar bursting neocortical cells (Blatow *et al.* 2003). Thus, synapses onto inhibitory interneurons could express either GluA2-lacking, Ca^{2+}-permeable AMPARs or GluA2-containing, Ca^{2+}-impermeable AMPARs (Fig. 1). However the rules dictating differential AMPAR subunit composition amongst distinct interneuron cohorts remained elusive. Of particular interest, in some cases, Ca^{2+}-impermeable and Ca^{2+}-permeable AMPAR complexes were shown to exist in the same interneuron (Toth & McBain, 1998; Sambandan *et al.* 2010). Indeed interneurons of the CA3 stratum lucidum localized Ca^{2+}-permeable AMPARs at synapses innervated by mossy fibre inputs and Ca^{2+}-impermeable AMPARs at synapses from CA3 associational fibres revealing a remarkable afferent input specificity to synaptic AMPAR composition in individual cells (Toth & McBain, 1998).

Preferred combinations of AMPAR subunits have functional consequences as subunit composition dictates ion selectivity and kinetic properties (Hume *et al.* 1991; Geiger *et al.* 1995; Koh *et al.* 1995; Traynelis *et al.* 2010). For example, GluA2-containing AMPARs possess a lower single channel conductance with slower gating properties relative to other AMPARs that lack the GluA2 subunit (Lomeli *et al.* 1994; Mosbacher *et al.* 1994; Swanson *et al.* 1997) and incorporation of GluA4 subunits dramatically increases channel kinetics (Swanson *et al.* 1997). GluA4 expression is high, while GluA2 expression is low in fast spiking PV-positive hippocampal interneurons (Geiger *et al.* 1995; Lambolez *et al.* 1996; Angulo *et al.* 1997; Pelkey *et al.* 2015) resulting in excitatory postsynaptic currents (EPCS) on PV interneurons with high Ca^{2+} permeability and an extremely rapid time course (Geiger *et al.* 1995, 1997; Lawrence & McBain, 2003) compared to EPSCs observed onto principal neurons (Hestrin, 1993). In addition, two alternatively spliced isoforms (flip

and flop) of each AMPAR subunit exist. The flop isoform yields receptors with more rapid gating properties and is the preferred isoform of AMPAR subunits in interneurons (Bochet *et al.* 1994; Geiger *et al.* 1995; Angulo *et al.* 1997). The expression of rapidly gating Ca^{2+}-permeable AMPARs in fast spiking interneurons is an important requirement for their ability to provide temporally precise control of network activity (for review see Bartos *et al.* 2007; Hu *et al.* 2014). Indeed fast-spiking PV-positive cortical interneurons show a correlation between action potential timing and miniature (m)EPSC half-width underscoring the importance of precise subunit expression for temporal precision in interneuron network dynamics (Helm *et al.* 2013). Moreover, findings in mice with genetically altered AMPAR subunit expression in interneurons have demonstrated the importance of specific subunit combinations for interneuron-mediated network entrainment (Table 1). For example, GluA2 overexpression in GAD67-positive interneurons altered the firing properties of the mutant interneurons and significantly disrupted long-range oscillation synchrony (Fuchs *et al.* 2001). In another study from the same group (Fuchs *et al.* 2007), elimination of either GluA1 or GluA4 subunits specifically in PV-positive interneurons compromised gamma frequency network oscillations and hippocampal working memory. The neuronal pentraxin 2/neuronal pentraxin receptor (NPTX2 and NPTXR), which belong to the neuronal pentraxin family, are expressed at glutamatergic synapses onto interneurons and cluster AMPARs (Xu *et al.* 2003; Sia *et al.* 2007). Mice with NPTX2/NPTXR loss of function exhibit severely reduced GluA4 expression in PV interneurons with concomitant alterations in gamma oscillations, sharp wave ripples measured *in vivo*, as well as impairing hippocampal working memory (Pelkey *et al.* 2015).

In cortical and hippocampal circuits, excitatory synaptic inputs either facilitate or depress in response to repetitive input (Reyes *et al.* 1998). In neuronal networks, paired-pulse depression (PPD) may help interneurons operate as coincidence detectors and permit firing at early time points in a train of ongoing activity, whereas paired-pulse facilitation (PPF) provides a mechanism to detect ongoing high frequency activity. PPD is common at synapses between pyramidal neurons and perisomatic targeting interneurons, such as pyramidal–multipolar PV interneuron synapses in neocortex (Reyes *et al.* 1998) and CA1 pyramidal–PV basket cell, –bistratified cell, and –cholecystokinin (CCK) cell synapses in hippocampus (Ali *et al.* 1998). In contrast PPF is observed at synapses between pyramidal neurons and dendrite targeting interneurons, such as CA1 pyramidal–oriens lacunosum-moleculare (OLM) interneuron synapses (Ali & Thomson, 1998; Reyes *et al.* 1998). Both types of plasticity are largely determined by presynaptic release properties. However, postsynaptic factors such as AMPAR desensitization and polyamine block can contribute to short-term plasticity. GluA2-lacking Ca^{2+}-permeable AMPARs are tonically blocked by endogenous intracellular polyamines at more positive membrane potentials producing their characteristic inwardly rectifying *I–V* relationship (Bowie & Mayer, 1995; Kamboj *et al.* 1995; Koh *et al.* 1995). Relief of this polyamine block is both use and voltage dependent (Bowie & Mayer, 1995; Rozov *et al.* 1998) and in interneurons either reduces the magnitude of paired-pulse depression or produces a facilitating response (Rozov & Burnashev, 1999). The degree of facilitation that results from relief of polyamine block is enhanced at more depolarized membrane potentials and presents a mechanism that can boost subthreshold excitatory inputs (Toth *et al.* 2000) providing a novel mechanism for synaptic gain.

NMDA receptors

Like AMPARs, NMDA receptors (NMDARs) are also remarkably diverse in their molecular composition, with various biophysical and pharmacological properties determined by the exact combination of subunits and splice variants incorporated into the native complex (McBain & Mayer, 1994; Traynelis *et al.* 2010). NMDARs are obligate heterotetramers with GluN1 being required for functional channels. Compared to AMPARs, NMDARs have much slower activation and deactivation kinetics and consequently their synaptic activation typically triggers a slower secondary component of synaptic input prolonging the window for temporal summation of excitatory events. Within NMDARs, GluN2A subunits promote the fastest kinetics while addition of GluN2B, GluN2C and GluN2D subunits slows channel kinetics with GluN1–GluN2D diheteromeric channels being the slowest (~2 s decay τ) (Vicini *et al.* 1998). NMDAR subunit expression varies across different brain regions, shows developmental regulation, and can be altered in disease states (Watanabe *et al.* 1992; Monyer *et al.* 1994; Akbarian *et al.* 1996; Purcell *et al.* 2001).

Initially, NMDARs were considered to minimally contribute to fast synaptic transmission in interneurons relative to their role in most principal cells (McBain *et al.* 1992; McBain & Dingledine, 1993; Monyer *et al.* 1994; He *et al.* 1998). However, more detailed analysis by various groups (Standaert *et al.* 1996; Lei & McBain, 2002; Matta *et al.* 2013; De Marco Garcia *et al.* 2015; von Engelhardt *et al.* 2015) showed that NMDAR contribution and subunit composition in interneurons varied based on interneuron subtype and interestingly appeared to correlate with the properties of AMPARs expressed in the same cell (McBain & Dingledine, 1993; Lei & McBain, 2002; Matta *et al.* 2013). For example, hippocampal mossy fibre–interneuron synapses expressing GluA2-lacking, Ca^{2+}-permeable AMPARs

Table 1. List of studies that used transgenic/knockout animals to study the significance of iGluR subunits in interneurons

iGluR subunit	Genetic modification	Interneuron subtype (mouse driver line)	Cellular physiology	Morphology	Cell number	Network	Behaviour	Reference
GluA1	Knockout	PV (PV-Cre)	Decreased AMPAR-mediated EPSCs.Altered firing.	N/A	N/A	Altered gamma frequency network oscillations.	Impaired spatial working memory, novel object recognition and response to spatial changes.	(Fuchs *et al.* 2007)
GluA2	Overexpression	GAD67	Altered firing properties.	N/A	N/A	Disrupted long-range oscillation synchrony.	—	(Fuchs *et al.* 2001)
GluA3	—	—	—	—	—	—	—	—
GluA4	Knockout	Global	Decreased AMPAR-mediated EPSCs.Altered firing.	N/A	N/A	Gamma frequency network oscillations altered.	Impaired spatial working memory. Novel object recognition and response to spatial changes.	(Fuchs *et al.* 2007)
GluN1	Knockout	PV (PV-Cre)	N/A	N/A	No change in hippocampus.	Hippocampal theta oscillations reduced and gamma oscillations increased, gamma-theta oscillation coupling altered.	Impaired object recognition and spatial memory.	(Korotkova *et al.* 2010)
	Knockout	Ppp1r2 (a protein phosphatase, expressed mostly in inhibitory interneurons) (Ppp1r2-Cre).	N/A	N/A	N/A	Increased firing rate of pyramidal neurons in cortex. Reduced synchronous activity.	Symptoms of schizophrenia: novelty-induced hyperlocomotion, mating and nest-building deficits, anhedonia-like and anxiety-like behaviours observed. Impaired social memory, spatial working memory and prepulse inhibition.	(Belforte *et al.* 2010)
	Knockout	Dlx5/6 (Dlx5/6-Cre introduced with viral infection).	N/A	Reduced dendrites and axons of cortical RE inter-neurons.No morphological change in VIP interneurons.	N/A	N/A	N/A	(De Marco Garcia *et al.* 2015)
GluN2A	Knockout	Dlx5/6 (Dlx5/6-Cre introduced with viral infection)	N/A	No change	N/A	N/A	N/A	(De Marco Garcia *et al.* 2015)

(Continued)

Table 1. Continued

iGluR subunit	Genetic modification	Interneuron subtype (mouse driver line)	Cellular physiology	Morphology	Cell number	Network	Behaviour	Reference
GluN2B	Knockout	GAD67	Reduced AMPAR-mediated mEPSC frequency, increased amplitude.	No change in str. oriens.	Normal PV cell number in barrel cortex.	Fatal neonatal seizures.	Reduced locomotor activity over time from birth to early death.	(Kelsch *et al.* 2014)
	Knockout	Olfactory granule cells(local deletion with viral infection).	Reduced excitatory synaptic contacts in proximal dendrite. Decreased frequency and amplitude of spontaneous excitatory postsynaptic current (sEPSCs).	Normal	Increased cell death of adult born granule cells.	N/A	N/A	(Kelsch *et al.* 2012)
	Knockout	Dlx5/6 (Dlx5/6-Cre introduced with viral infection)	N/A	Reduced dendrites and axons of cortical RE inter-neurons.No change in VIP interneurons.	N/A	N/A	N/A	(De Marco Garcia *et al.* 2015)
GluN2C	—	—	—	—	—	—	—	—
GluN2D	Knockout	Global	No change in decay τ of NMDAR-mediated EPSCs after ifenprodil treatment in hippocampal interneurons.	N/A	N/A	N/A	N/A	(von Engelhardt *et al.* 2015)
GluN3A	—	—	—	—	—	—	—	—
GluN3B	—	—	—	—	—	—	—	—
GluK1	Knockout	Global	Kainate can still activate an inward current insensitive to AMPAR blockers in CA1 str. radiatum interneurons, and increased spontaneous inhibitory postsynaptic current (sIPSC). Frequency in CA1 pyramidal cell (PC) similar to wild-type.	N/A	N/A	N/A	N/A	(Mulle *et al.* 2000)
	Knockout	Global	Kainate did not increase sIPSC amplitude and frequency in CA3 str. radiatum interneurons, but reduced eIPSCs similar to wild-type.	N/A	N/A	Enhanced kainate-induced gamma oscillations.	N/A	(Fisahn *et al.* 2004)
GluK2	Knockout	Global	Kainate can still activate an inward current in CA1 str. radiatum interneurons. Kainate leads to a rapid and reversible decrease in the amplitude of eIPSCs in CA1 pyramidal neurons, similar to wild-type.	N/A	N/A	N/A	N/A	(Mulle *et al.* 2000)

(Continued)

Table 1. Continued

iGluR subunit	Genetic modification	Interneuron subtype (mouse driver line)	Cellular physiology	Morphology	Cell number	Network	Behaviour	Reference
	Knockout	Global	Kainate did not activate an inward current in CA3 str. radiatum interneurons, and increased sIPSC amplitude and frequency in PC, similar to wild-type, but did not change eIPSCs.	N/A	N/A	Disrupted kainate-induced gamma oscillations.	N/A	(Fisahn *et al.* 2004)
GluK1/2	Knockout	Global	Kainate-activated inward current is eliminated in CA1 str. radiatum interneurons, and does not increase sIPSC frequency, and does not affect eIPSC amplitude in CA1 PC.	N/A	N/A	N/A	N/A	(Mulle *et al.* 2000)
NPTX2 (NARP)	Knockout	Global (PV interneurons studied).	Activity-dependent scaling of excitatory input on hippocampal PV interneurons is lost.	N/A	N/A	Decreased spontaneous firing rate of PV interneurons. Mice became hypersensitive to kindling-induced seizures.	N/A	(Chang *et al.* 2010)
	Knockout	Global (PV interneurons studied).	Connectivity between layerII/III pyramidal neurons to PV interneurons reduced as well as the release sites and probability.	N/A	N/A (Note: cortical macroorganization normal.)	Increased neuronal excitability in visual cortex.Impaired ocular dominance plasticity (critical period plasticity). Visual acuity normal: experience-dependent enhancement of the VEPs (visually evoked potentials) contralateral bias and experience-dependent enhancement of VEP amplitudes in response to high-frequency visual stimulation persist.	N/A	(Gu *et al.* 2013)
NPTX2/ NPTXR	Knockout	Global (PV interneurons studied).	Lost or severely reduced GluA4 expression in hippocampal PV interneurons. Reduced AMPA/NMDA current ratio along with amplitude and frequency of sEPSCs in PV interneurons. Increased decay τ of sEPSCs.	Basket cell dendritic morphology normal.	N/A	Reduced feedforward inhibition of hippocampal pyramidal neurons reduced.Increased time window of giant depolarizing potential occurrence. Impaired gamma oscillations recorded from acute slices or awake animal brains. Impaired sharp wave ripples *in vivo*. Enhanced epileptic activity.	Impaired hippocampal working memory.	(Pelkey *et al.* 2015)

typically contain GluN2B-rich NMDARs with slow decay kinetics. Conversely, mossy fibre–interneuron synapses that comprise GluA2-containing, Ca^{2+}-impermeable AMPARs tend to coexpress NMDARs with relatively faster decay kinetics and larger amplitudes (Lei & McBain, 2002).

Unlike principal cells, Ca^{2+} influx into interneurons can potentially occur via both AMPA and NMDA receptors, depending on the iGluR subunit composition within a given synapse. As a general rule, in the CA1 hippocampus, interneuron synapses that comprise Ca^{2+}-permeable AMPARs (Fig. 1*C*, *E* and *G*) express low levels of synaptic NMDARs as reflected by a low NMDA/AMPA receptor-mediated current amplitude ratio (∼1:5; Fig. 1*C* and *H*) (Matta *et al.* 2013). In contrast, interneurons dominated by Ca^{2+}-impermeable AMPARs (Fig. 1*D* and *F*) have larger NMDAR-mediated currents with higher NMDA/AMPA ratios (∼1:1; Fig. 1*D* and *G*) (Lei & McBain, 2002; Matta *et al.* 2013; De Marco Garcia *et al.* 2015).

Similar to AMPARs, NMDAR subunit expression also varies among interneuron subtypes. Both GluN2A and GluN2B subunits of NMDARs are expressed in GABAergic interneurons. GluN2A-containing or GluN2B-containing NMDARs can be identified based on decay time constant and subunit-selective NMDAR antagonists (i.e. ifenprodil, Ro 25-6981, NVP-AAM077) (Fig. 2). In juvenile rat brain, Ca^{2+}-permeable AMPARs at mossy fibre–CA3 interneuron synapses have NMDARs with slow kinetics and are strongly blocked by ifenprodil, consistent with a high GluN2B subunit expression. In contrast, mossy fibre–CA3 interneuron synapses comprising Ca^{2+}-impermeable AMPARs typically have NMDARs with faster kinetics and less sensitivity to ifenprodil suggesting a lower GluN2B and higher GluN2A content (Lei & McBain, 2002). CA1 interneurons of mice at comparable ages typically express NMDARs with fast kinetics (Fig. 2*B* and *E*) and low ifenprodil sensitivity (Fig. 2*B* and *F*) (i.e. GluN2A-containing) at synapses containing Ca^{2+}-permeable AMPARs and NMDARs with slower kinetics (Fig. 2*D* and *E*) and high ifenprodil sensitivity (Fig. 2*D* and *F*) (i.e. GluN2B-containing) at synapses expressing Ca^{2+}-impermeable AMPARs (Matta *et al.* 2013). Thus, different rules for particular subunit expression may exist across different synapses onto different interneuron subtypes, or as we shall discuss below NMDAR subunit expression can show differential developmental regulation, which depends on interneuron identity. Compared to GluN2A and GluN2B, very little is known about GluN2C and GluN2D subunit expression in interneurons. *In situ* hybridization showed the presence of GluN2D in cortical and hippocampal PV-, somatostatin (SOM)-, CB- and calretinin (CR)-positive interneurons as well as in VIP-positive irregular spiking interneurons (Monyer *et al.* 1994; Porter *et al.* 1998; von Engelhardt *et al.* 2015). Indeed, blocking NMDAR activity by ifenprodil increased the decay time constant of the synaptic currents in wild-type mice at only early ages, whereas the same treatment did not change the decay kinetics of the currents in GluN2D knockout mice suggesting early expression of GluN2D by some hippocampal interneurons (Table 1) (von Engelhardt *et al.* 2015). The expression of slow gating GluN2B- and GluN2D-dominated NMDARs early in development probably provide a wider temporal window for synaptic integration potentially important for network maturation, whereas GluN2A expression at later ages enhances the precision of synaptic responses.

Although somewhat controversial, NMDARs have also been posited to exist on the presynaptic terminals of various synapses including those between pyramidal cells and interneurons, where they are thought to regulate synaptic transmission and information flow (Duguid, 2013) in a target-specific manner. For example, in layer V of developing mouse visual cortex, activation of presynaptic NMDARs modulates release probability between pyramidal and Martinotti cells but not at pyramidal to basket cell synapses (Buchanan *et al.* 2012). Similarly, activation of presynaptic NMDA receptors facilitates inhibition at multipolar interneuron to pyramidal cell synapses but not at bitufted to pyramidal cell synapses (De-May & Ali, 2013) in neocortical layers II–V.

Despite the relatively small contribution of NMDARs to synaptic transmission in a number of interneuron subtypes (e.g. PV-positive interneurons) physiological roles have been described at cellular (Lei & McBain, 2002; Kelsch *et al.* 2012, 2014; Matta *et al.* 2013), network (Korotkova *et al.* 2010; Kelsch *et al.* 2014) and behavioural levels (Belforte *et al.* 2010). In synapses containing either high or low NMDAR/AMPAR ratios, pharmacological blockade of NMDARs decreased action potential firing in response to stimulus trains by decreasing temporal summation of excitatory events (Lei & McBain, 2002). At Ca^{2+}-impermeable mossy fibre–interneuron synapses, which exhibit high NMDAR/AMPAR ratios, a train of stimuli triggers multiple action potentials at each stimulus followed by a large late NMDAR-dependent depolarizing envelope that persisted long after the stimulus. In contrast, in synapses with low NMDAR/AMPAR ratios, EPSPs triggered only single action potential firing with no substantial after-depolarizing phase (Lei & McBain, 2002). In the MGE-derived hippocampal interneurons of newborn mice, blocking GluN2B similarly modulated EPSP-driven action potential firing (Matta *et al.* 2013).

An instructive role for NMDAR activity in the circuit integration of developing interneurons is suggested by the finding that genetic deletion of GluN2B selectively within interneurons leads to a reduction in the frequency of AMPAR-mediated mEPSCs in hippocampal interneurons (Fig. 3*A* and *B*; Table 1) (Kelsch *et al.* 2014). This decreased excitatory drive promoted hippocampal

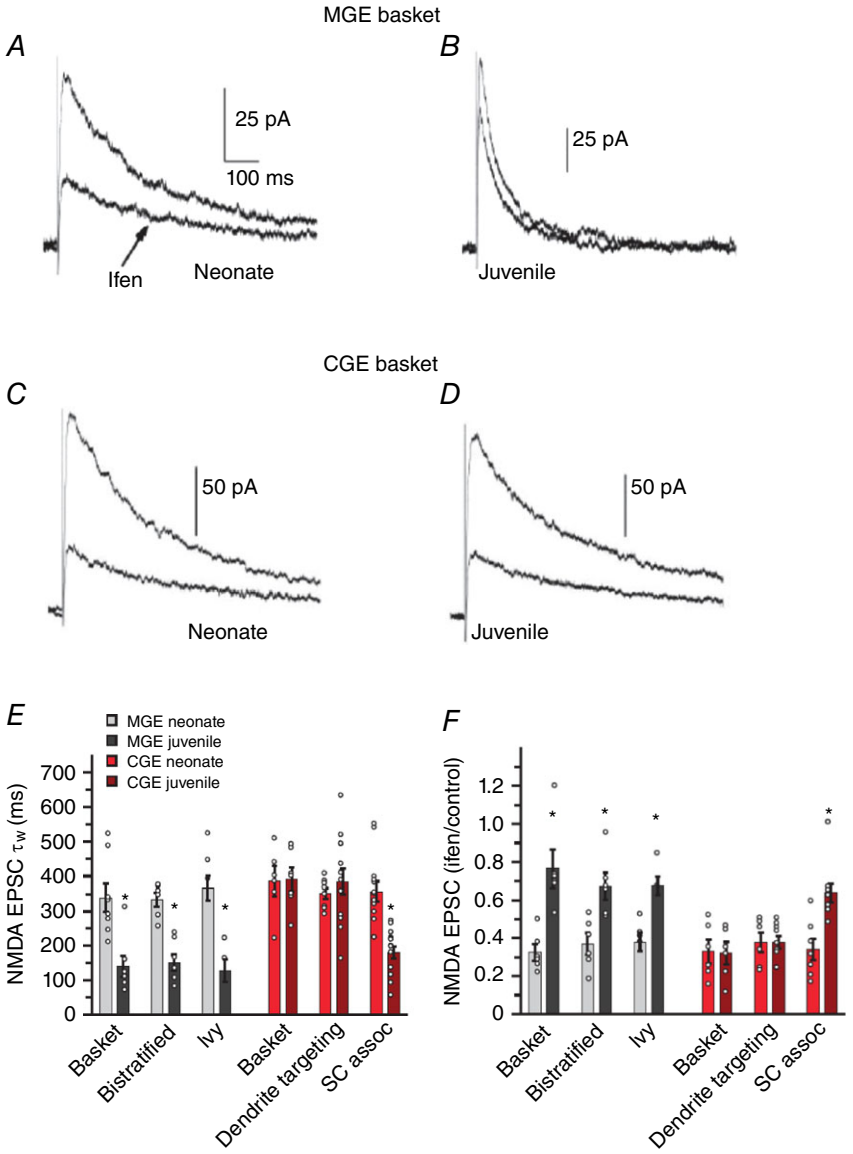

Figure 2. NMDAR subunit expression in MGE-derived hippocampal interneurons show developmental regulation
A–D, channel gating of NMDARs accelerates and loses GluN2B antagonist (ifenprodil) sensitivity in MGE-derived interneurons whereas NMDARs in CGE-derived interneurons have properties that persist through development. The traces are representative evoked NMDAR-mediated EPSCs recorded at +40 mV holding potential from MGE-derived basket cells (*A* and *B*) and CGE-derived basket cells (*C* and *D*) from a neonate (*A* and *C*) and a juvenile (*B* and *D*) upon Schaffer collateral stimulation in the absence (upper traces) or presence (lower traces) of ifenprodil. In both MGE- and CGE-derived basket cells of neonate (*A* and *C*), the peak amplitude of the current is markedly reduced indicating GluN2B-rich NMDARs in these interneurons. Similar antagonist application is unable to reduce evoked current in MGE-derived basket cell of juvenile indicating a significant loss of GluN2B subunits from NMDAR pool in this synapse. Juvenile NMDAR currents also possess faster kinetics than neonate consistent with a GluN2B–GluN2A switch (*B*). In contrast ifenprodil block is significant in CGE-derived basket cell across both developmental time points indicating that NMDA receptor subunit expression does not undergo developmental regulation in CGE-derived interneurons (*D*). *E*, graph summarizes the detailed analysis of the NMDAR EPSC decay kinetics weighted time constant (τ_w) for both neonate and juvenile MGE- and CGE-derived interneurons at two different developmental time points, neonate (P6–9) and juvenile (P17–21). *F*, graph summarizes the detailed analysis of the developmental regulation of ifenprodil sensitivity expressed as the ratio of the NMDAR EPSC peak amplitude measured in the presence of ifenprodil divided by the control NMDA EPSC peak amplitude. Reproduced from Matta *et al.* (2013) with permission from the authors.

seizures and subsequent lethality (Table 1) (Kelsch *et al.* 2014). Selective ablation of NMDARs later in development in PV-positive interneurons alters theta and gamma oscillations indicating a critical role for NMDARs in PV–interneuron-mediated circuit entrainment (Table 1) (Korotkova *et al.* 2010). These same mice, together with another transgenic model in which loss of NMDARs is more widespread among interneurons (Table 1) (Belforte *et al.* 2010), also showed impairments in spatial and short- and long-term memory tests. Furthermore, loss of NMDARs in cortical GABAergic interneurons at early postnatal ages triggered several behavioural deficits associated with schizophrenia including psychomotor agitation, anhedonia, reduced prepulse inhibition of acoustic startle, deficits in nesting/mating, and social withdrawal (Belforte *et al.* 2010) supporting the NMDAR hypofunction theory of schizophrenia (for reviews see Coyle, 1996, 2012).

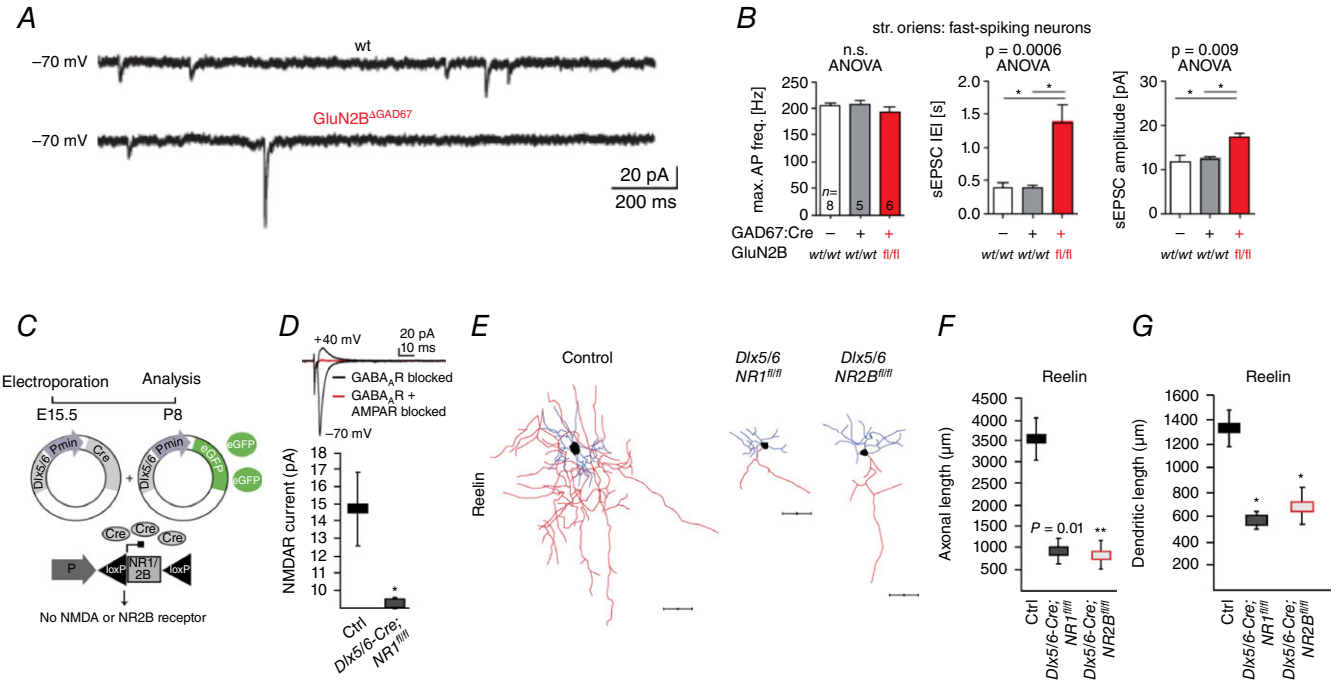

Figure 3. Genetic deletion of NMDARs reveals control of both synaptic and anatomical properties
A and *B*, genetic deletion of the GluN2B subunit of NMDARs results in abnormal maturation of glutamatergic synapses in hippocampal interneurons. In the transgenic line the gene coding for GluN2B is flanked with loxP cassettes and deleted upon breeding with GAD67:Cre mice. *A*, representative traces of spontaneous EPSCs from wild-type (wt; upper trace) and GluN2B knockout (GluN2B$^{\Delta GAD67}$; lower trace) fast spiking GAD67-positive interneurons in stratum oriens. In GluN2B knockout interneurons, there is an apparent reduction in spontaneous events, as well as large amplitude events indicating that the number of active synapses has decreased while more AMPARs are incorporated into those remaining. *B*, graphs show the group data for analysis of the firing properties of the wild-type and knockout interneurons (left), interspike intervals of spontaneous (s)EPSCs as representation of event frequency (IEI, middle), and mean amplitude of events (right). *C–G*, loss of either all NMDARs or only the GluN2B subunit alone in cortical interneurons results in abnormal anatomy. *C*, the genetic strategy to create the conditional knockout animals. Both transgenic animal and virus technology were used to knock out all or the GluN2B-rich subgroup of NMDARs in CGE-derived cortical interneurons. The genes coding for GluN1 or GluN2B were deleted in Dlx5/6-expressing interneurons of targeted knockin mice in which the genes coding for GluN1 or GluN2B are flanked with loxP cassettes. Upon electroporation of viruses that carry the Cre-expressing sequence downstream of Dlx5/6 promoter, *glun1* or *glun2b* gene deletions occur. (E, embryonic day.) *D*, the traces are representative evoked EPSCs at −70 mV (inward current) and +40 mV (outward current, black trace and no current, red trace) holding potentials show the loss of NMDAR-mediated currents (red trace) in GluN1-knockout interneurons. The graph below shows the group data. *E*, reconstructions of reelin-positive interneurons of wild-type (left), GluN1- (middle) and GluN2B- (right) knockout mice. Both GluN1 and GluN2B loss result in shrinkage of dendrites and axons in RE-positive cortical interneurons and GluN2B loss is enough to create this anatomical abnormality. Scale bars, 50 μm. Axons are shown in red, dendrites in blue. The data are summarized with the graphs for axonal (*F*) and dendritic (*G*) length analysis of the RE-positive interneuron morphology. *A* and *B* are reproduced with permission from Kelsch *et al.* (2014). *C–G* are reproduced with permission from De Marco Garcia *et al.* (2015).

Kainate receptors

Of the ionotropic glutamate receptors, kainate receptors (KARs) on inhibitory interneurons have received much less attention and consequently little clarity exists regarding their expression profiles and functional role(s). KARs are homo- or heteromeric tetramers composed of GluK1 (GluR5) (Bettler *et al.* 1990), GluK2 (GluR6) (Egebjerg *et al.* 1991), GluK3 (GluR7) (Bettler *et al.* 1992), GluK4 (KA1) or GluK5 (KA2) subunits (Werner *et al.* 1991; Herb *et al.* 1992; Sakimura *et al.* 1992; for review see Traynelis *et al.* 2010). KAR subunits are expressed widely in brain (Wisden & Seeburg, 1993) and interneurons are particularly enriched with both GluK1, GluK2 and GluK4 (Bureau *et al.* 1999; Paternain *et al.* 2000; Fisahn *et al.* 2004; Lein *et al.* 2007) where they act to regulate both pre- and postsynaptic activity (for review see Carta *et al.* 2014). Both pharmacological and genetic tools have been used to dissect the roles of particular KAR subunits in interneurons; however, conflicting results have often arisen (Table 1) (Bureau *et al.* 1999; Mulle *et al.* 2000; Fisahn *et al.* 2004; Maingret *et al.* 2005) due in part to poor receptor-selective pharmacology and the non-selective targeting of specific subpopulations of hippocampal interneurons, which probably show different KAR subunit expression profiles (Bureau *et al.* 1999; Maingret *et al.* 2005; Wondolowski & Frerking, 2009).

Evoked or spontaneous synaptic events mediated by KARs on inhibitory interneurons have been reported in only a small number of studies (Cossart *et al.* 1998; Frerking *et al.* 1998; Cossart *et al.* 2002; Frerking & Ohliger-Frerking, 2002; Wondolowski & Frerking, 2009). In most of these studies the KAR-mediated component of the synaptic event appears as a small slow tail current in the EPSC waveform reminiscent of that seen on principal cells. The clearest example of a pure KAR-mediated synaptic event was demonstrated in recordings of spontaneous synaptic activity in interneurons of the CA1 stratum oriens, primarily OLM cells (Cossart *et al.* 2002; Goldin *et al.* 2007). In these studies quantal synaptic events mediated by KARs were observed which were slow (decay τ ~10 ms) compared to pure AMPA-mediated synaptic events and represented a sizeable fraction of the total spontaneous EPSC population (~30%). This study was the first to suggest that excitatory synapses onto interneurons may target KARs and AMPARs to distinct synaptic compartments. Attempts by others to replicate these observations, however, have proven difficult. Oren *et al.* (2009) in contrast concluded that the vast majority of spontaneous EPSCs in stratum oriens OLM cells observed at negative holding potentials arose via AMPA receptor activation with no evidence for KAR-mediated events (see also Wondolowski & Frerking, 2009). Indeed, evoked GluK1-containing KAR synaptic events were observed to make only a modest contribution (~10% of the total current) when synaptic transmission was driven by repetitive activity (Oren *et al.* 2009), further questioning their functional significance. Regardless, KAR-induced inward currents triggered by exogenous agonist application have been identified in numerous inhibitory interneuron studies indicating that functional KARs reside in the postsynaptic compartment, despite the paucity of evidence for synaptic KAR events and comprise either GluK1 or GluK2 subunits (Cossart *et al.* 1998; Frerking *et al.* 1998; Paternain *et al.* 2000; Fisahn *et al.* 2004; Oren *et al.* 2009; Wondolowski & Frerking, 2009) or both (Porter *et al.* 1998; Mulle *et al.* 2000; Paternain *et al.* 2000). Activation of postsynaptic KARs by exogenous agonists depolarizes interneurons, increasing their action potential firing rate, resulting in an increased inhibitory drive onto pyramidal cells (Cossart *et al.* 1998; Frerking *et al.* 1998). KAR-evoked inward currents are absent in CA3 stratum radiatum interneurons in GluK2 loss of function mice but persists in GluK1 knockouts consistent with a prominent role for GluK2-containing KARs on specific populations of interneurons (Fisahn *et al.* 2004) while in CA1 stratum radiatum interneurons kainate could evoke inward currents in either of the single GluK1 or GluK2 loss of function mice but not in the double GluK1/GluK2 knockout (Mulle *et al.* 2000).

In hippocampal slices, exogenous kainate application reduces evoked IPSC (eIPSC) amplitudes and increases failures of eIPSCs onto CA1 pyramidal neurons, as well as decreasing miniature (m)IPSC frequency onto interneurons (Clarke *et al.* 1997; Rodriguez-Moreno *et al.* 1997; Bureau *et al.* 1999; Cossart *et al.* 2001; Maingret *et al.* 2005) indicating a role for presynaptic KARs in the regulation of GABA release onto CA1 pyramidal neurons (however, cf. with Frerking *et al.* 1999; Cossart *et al.* 2001; Fisahn *et al.* 2004). Paired electrophysiological recordings between CCK-positive interneurons and pyramidal cells, PV-positive interneurons and pyramidal cells, and CCK-positive- and PV-positive interneurons, revealed that depression of unitary IPSCs by kainate is observed only at connections between CCK-positive interneurons and pyramidal cells through a mechanism involving GluK1-containing KARs (Daw *et al.* 2010). In a parallel study, high frequency stimulation of Schaffer collateral afferents in CA1 resulted in a small transient depression of inhibitory transmission onto pyramidal cells that arises through glutamate spillover activating presynaptic GluK1-containing receptors on cannabinoid receptor 1 (CB1)-positive interneuron presynaptic terminals (Min *et al.* 1999). This spillover mechanism appears to rely on the concerted activation of both the endocannabinoid system and presynaptic CB1 receptors and GluK1 KARs (Lourenco *et al.* 2010). Of particular interest transmission between CCK-positive interneurons and their downstream targets arises through both synchronous and asynchronous transmitter release. At these synapses KAR

activation depresses only the synchronous component of GABA release leaving asynchronous release unchanged (Daw *et al.* 2010). Thus presynaptic KAR activation may act to simultaneously reduce 'conventional' GABA transmission occurring via synchronous release, while preserving the influence of tonic inhibition driven by asynchronous release during periods of intense activity.

Dissecting the role(s) of KARs in shaping inhibitory interneuron activity is far from complete and will require both better pharmacological tools and targeted disruption of specific KAR subunit function in identified cohorts of inhibitory interneurons. The paucity of clear roles for synaptic KARs coupled to the small amplitudes of the conductances that have been described cast considerable doubt as to whether these receptors are performing a critical, if any, physiological role in inhibitory interneurons. However, Goldin *et al.* (2007) have demonstrated that KARs, but not AMPARs, on SOM-positive OLM cells are critical for spike entrainment at theta frequencies, suggesting they are important in part for oscillatory activity.

Developmental plasticity of iGluR subunit expression

iGluR subunit expression profiles are subject to regulation through both developmental and activity dependent mechanisms in a number of cell and synapse types (Monyer *et al.* 1991; Liu & Cull-Candy, 2000; Kelsch *et al.* 2012, 2014; Matta *et al.* 2013; von Engelhardt *et al.* 2015). Three (GluA1–3) of the four AMPAR subunits are expressed at embryonic stages of the developing cortex, whereas the GluA4 subunit appears only postnatally (Bettler *et al.* 1990; Monyer *et al.* 1991; Geiger *et al.* 1995; Pelkey *et al.* 2015). Although the rectification index of AMPARs changes at Ca^{2+}-permeable AMPAR synapses of neonatal cortical pyramidal neurons over development (Kumar *et al.* 2002; Ho *et al.* 2007), there is no evidence for developmental regulation of GluA2 expression in interneurons at Schaffer collateral–CA1 interneuron synapses (Fig. 1*H*) (Matta *et al.* 2013). In contrast, GluN2 subunit expression is highly dynamic in the entire brain during development (Monyer *et al.* 1994). The most comprehensive and detailed analysis of glutamatergic synapse maturation in interneuron development is presented by Matta *et al.* (2013). In this study, interneuron populations in the hippocampal CA1 region were studied based on their origins within either the medial (MGE) (Fig. 1*A*) or caudal ganglionic eminences (CGE) (Fig. 1*B*) of the ventral telencephalon (Lee *et al.* 2010; Tricoire *et al.* 2011). Schaffer collateral synapses onto MGE-derived interneurons (e.g. PV-, SOM- and neuronal NO synthase (nNOS)-positive interneurons) typically express Ca^{2+}-permeable, GluA2-lacking AMPARs (Fig. 1*C*, *E* and *H*) whereas CGE-derived interneurons (CR, VIP, CCK, reelin (RE) and some nNOS interneurons) mostly express Ca^{2+}-impermeable, GluA2-containing AMPARs (Fig. 1*D*, *F* and *H*). These origin-specific AMPAR profiles are consistent across a broad developmental age range and show no developmental regulation of GluA2 expression. In contrast NMDARs at synapses onto MGE-derived interneurons switch from initially expressing NMDARs with slow kinetics and high ifenprodil sensitivity (Fig. 2; Table 1) to ifenprodil-resistant fast NMDARs, indicating a developmental subunit switch from GluN2B- to GluN2A-dominated receptors. This developmental NMDAR subunit switch can also be triggered by high frequency stimulation and such acute plasticity requires a rise in intracellular Ca^{2+} (perhaps through Ca^{2+}-permeable AMPARs) but occurs independent of either activation of NMDARs themselves or metabotropic mGluR5 (which are required for a similar subunit switch in pyramidal cell synapses; Matta *et al.* 2011, 2013). In contrast Schaffer collateral synapses onto almost all CGE-derived interneuron subtypes express GluN2B-containing NMDARs across all developmental stages tested and do not exhibit any acute plasticity following high frequency stimulation (Matta *et al.* 2013). Thus far no attempt has been made to address the developmental expression or profiles of KAR subunit expression on inhibitory interneurons derived from either the MGE or CGE.

The role of iGluRs in development and maturation of interneurons

Embryonic expression of both AMPA and NMDA receptor subunits raises the question of whether iGluRs participate in cellular migration and anatomical maturation. Cortical interneurons originate in the ventral telencephalon and migrate tangentially through the neocortex and into the primordial hippocampus. They then move radially to reach their particular cortical or hippocampal layer of choice (Marin *et al.* 2010). A number of *in vitro* (Behar *et al.* 1999) and *in vivo* (Manent *et al.* 2006; Bortone & Polleux, 2009) studies have proposed a role for NMDARs (Bortone & Polleux, 2009) or AMPARs (Manent *et al.* 2006) in GABAergic interneuron migration based on changes in cell migration observed following pharmacological antagonism of AMPA and NMDA receptors. However, the density of PV-positive interneurons in the somatosensory cortex of transgenic mice with selective deletion of GluN2B from GAD67-positive interneurons was comparable to that of wild-type mice (Table 1) (Kelsch *et al.* 2014). In contrast similar genetic manipulation resulted in increased cell death in the adult born granule cell population of the olfactory bulb (Table 1) (Kelsch *et al.* 2012), indicating that these NMDARs serve different roles for cell survival in different brain regions or developmental stages. It is evident that glutamate also serves as a chemoattractant for

cellular migration (Behar *et al.* 1999); however, conflicting results about the functional importance of AMPA and NMDARs require additional and better approaches to the question.

Anatomical maturation of specific subpopulations of interneurons is also influenced by glutamate receptor expression (De Marco Garcia *et al.* 2015). Fishell and colleagues demonstrated that elimination of GluN1 and GluN2B, but not GluN2A, in cortical CGE-derived interneurons produced cell type-specific (RE-positive only, but not VIP-positive) deficits in dendritic and axonal morphology (Fig. 3*C–G*; Table 1). Similarly, increased expression of fast mEPSCs as a consequence of overexpression of a postsynaptic scaffolding protein, SAP97, in cortical PV cells has been shown to be correlated with increased dendritic complexity and additionally alter passive and active membrane properties (Akgul & Wollmuth, 2013). In general, activity is considered an important factor for proper interneuron morphological maturation as blunting membrane excitability by overexpression of inwardly rectifying potassium channels stunts interneuron morphological differentiation (De Marco Garcia *et al.* 2011). Therefore, whether the anatomical alterations of the interneurons in these models are a result of changes in neuronal activity or removal of GluRs *per se* is currently unknown.

Conclusions and unanswered questions

The issues discussed in this review highlight recent research on iGluR diversity and its regulation in different interneuron subtypes. Although accumulating evidence provides some general rules for excitatory input onto interneurons, clear exceptions to these general rules exist suggesting that a complicated interplay between receptors and downstream signalling cascades operate within distinct cell populations and at discrete inputs onto individual interneurons. Of particular interest, a picture is emerging whereby receptor subunit expression and AMPA:NMDAR expression profiles within interneuron populations derived from common embryonic lineages share common rules and are regulated in a precise spatiotemporal manner by specific cellular and extracellular molecules. However, many details critical for our complete understanding of the role iGluRs play in determining interneuron function remain untested or unanswered. A short list of those we feel are the most pertinent include:

(1) Many iGluR subunits are expressed at embryonic ages (Bettler *et al.* 1990; Monyer *et al.* 1991, 1994; Herb *et al.* 1992; Allen Brain Atlas; http://mouse.brain-map.org/; Pelkey *et al.* 2015); however, there is a paucity of information regarding what role iGluRs play (if any) during a period when cells are migrating and incorporating into the emerging cortical circuit. Embryonic expression of iGluRs is particularly intriguing given the fact that functional glutamatergic synapse development does not occur typically until early postnatal days (Ben-Ari, 2014). Whether these receptors detect environmental glutamate gradients and drive cellular migration during embryonic development is unknown.

(2) Interneurons derived from the MGE or CGE require the concerted action of numerous transcription factors, (e.g. Nkx2.1, Dlx1/2/5/6, Lhx6 etc.) to determine cell fate and identity (Kessaris *et al.* 2014). Lineage analysis suggests that early specification of cells sets in motion a concerted programme of gene expression that will ultimately determine the cells' function and role in the emerging neural network. For example, in PV-positive interneurons upregulation of both kinetically fast Na^+ and K^+ voltage-gated channels, the calcium-binding protein parvalbumin, syt2, a presynaptic regulator of synaptic transmission, as well as acquisition of synapses comprising GluA1/4 heteromers and an NMDAR subunit switch all occur within a tight window during the second week of postnatal life. This suggests that the acquisition of 'fast-spiking' and rapid synaptic transmission onto and from PV-positive interneurons results from a tightly regulated and concerted gene expression programme that is held in check until postnatal week 2. How this concerted expression is achieved is at present unclear. Furthermore, one might imagine a scenario where perturbation of any one of these important proteins could impact the expression profiles of all others leading to widespread defects in a number of interrelated proteins.

(3) The small amplitude and limited role in synaptic transmission of the NMDAR conductance at Schaffer collateral synapses onto MGE-derived interneurons is puzzling. Indeed of all interneurons studied PV-positive interneurons have perhaps the smallest observable NMDAR conductance (Matta *et al.* 2013). Of interest, loss of function of NMDAR in PV-positive interneurons early in development has suggested an NMDAR-dependent hypofunction model of schizophrenia (Nakazawa *et al.* 2012) that is not completely recapitulated when NMDARs are eliminated later on in life. This puzzling observation is hard to reconcile with the limited synaptic NMDAR currents typically triggered in these cells and suggests that alternative roles for NMDARs other than conventional synaptic transmission must exist in these cells early in development.

(4) GluN2B and GluN2A subunits are differentially expressed during MGE-derived interneuron maturation (with GluN2B predominating early in

development) (Matta *et al.* 2013). One could hypothesize that a loss of GluN2B early in development would have a major impact on many aspects of cell migration and maturation into the nascent cortical circuit (whereas embryonic elimination of GluN2A would have a more limited impact). Moreover, GluN2B and GluN2A are selectively expressed at mature Schaffer collateral synapses onto CGE- *versus* MGE-derived interneurons, respectively, suggesting distinct roles for both types of NMDARs. In addition, each of these subunits confer distinct biophysical properties on the native receptor and have preferred cytoplasmic binding partners and cell signalling cascades. Targeted elimination of particular GluN subunits on specific cohorts of interneurons is required to allow us to unravel the intricate roles played by each of these subunits in determining interneuron maturation and circuit function.

(5) The need to identify clear role(s) for post-synaptic KARs on interneurons. Are kainate receptors functionally relevant or are they an evolutionary vestige whose limited conductance plays only a minor role in sculpting transmission onto or off interneurons?

(6) Finally, what are the roles for GluRs on interneurons in the development of human pathological phenotypes? A number of genome-wide association studies (GWAS) highlight GluR subunits and interacting proteins expressed on particular interneuron subtypes that may provide clues to the roles played by interneuron dysfunction in these pathologies. However, while the use of traditional global or conditional knockout strategies are helpful, they are limited in providing only a cursory understanding of diseases related to the dysregulated expression and function of these receptors in particular cell types (Yuan *et al.* 2015). With the emergence of advanced genome engineering technologies like CRISPR/Cas9 (Hsu *et al.* 2014), it will be possible (and easier) to target specific genomic DNA sequences in relevant interneuron cohorts to generate new transgenic/knockout lines within a short period of time. iGluR mutations observed in human neural circuit disorders could potentially be recapitulated in animal models to permit the targeted study of clinically relevant neurological diseases and possibly lead to the generation of specific therapeutic intervention.

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Additional information

Competing interests

None declared.

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