A role for GABAergic interneuron diversity in circuit development and plasticity of the neonatal cerebral cortex

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Abstract

GABAergic interneurons are a highly heterogeneous group of cells critical for the mature function and development of the neocortex. In terms of the latter, much attention has focused on the well-established role of parvalbumin (PV+)-expressing, fast spiking, basket cells in determining the critical period plasticity. However recent endeavours have started to shed the light on the contribution of other interneuron subtypes to early circuit formation and plasticity. Data that suggest that there are significant interactions between PV+ cells and other interneuron subtypes that regulate circuit development in rodents in the first postnatal week. Moreover a number of these early interactions are transient which points to an important, distinct role for interneuron diversity in setting up emergent neocortical processing.

Highlights

- Interneuron diversity is established at the moment of neurogenesis.
- All interneuron subtypes contribute to early neonatal circuit formation.
- The interaction between interneuron subtypes is likely important for plasticity.
- These early interneuron circuits can be distinct from those present in adults.

Introduction

Locally-projecting GABAergic interneurons arise from diverse neurogenic niches in the ventral ganglionic eminences of the telencephalon before tangentially migrating to populate the entire rostral-caudal extent of the developing pallium. Over the last decade *in vitro*, transplant and developmental genetic approaches have determined that the fate of cortical interneurons is largely dependent on the temporal and spatial origin of the interneuron [1-7]. This suggests that the basic logic of the GABAergic system – the array of diverse subtypes critical to cognitive processing in the mature brain [8-11] – is established early in life; a time point at which the influence of GABA neurotransmission of post-synaptic neurons undergoes a change in signal[12, 13]. While research to date has focused primarily on the role of glutamatergic neurons in emerging neonatal circuits [14, 15], these do not act in exclusion, with GABAergic interneurons having an important role in sculpting and controlling early activity [16, 17]. This review focuses on recent evidence that suggests that interneuron diversity is important for defining circuits and network plasticity in the neonatal rodent brain. Dissections of these contributions are vital given the relationship between a number of these cells types and neurodevelopmental psychiatric disorders [18-20].

A prolonged time window for early circuit formation

In the mature neocortex GABAergic interneurons can at a basic level be broken down into three main populations defined by expression of the calcium-binding protein parvalbumin (PV+), the neuropeptide somatostatin (SST+) and the serotonin ionotropic receptor (5-HT_3R)[21]. Two of these populations – SST+ and 5-HT_3R subtypes – show a bias in distribution across the depth of the cortex; being preferentially found in infragranular and supragranular layers respectively [21-26]. This distribution likely reflects their respective temporal origin [27] with SST+ interneurons born early in the medial ganglionic eminence (MGE) [4] whereas 5-HT_3R subtypes are born later from the caudal ganglionic eminence (CGE) [6, 28] (Figure 1). PV+ cells originate from the MGE and are born across a broad temporal window. Even in rodents, the protracted nature of neurogenesis and migration means that GABAergic interneurons are arriving in the dorsal pallium as early as embryonic day 12 (E12) [29] but with some cells not sorting into their final destination layers for at least another two weeks [27]. At the onset of circuit formation around birth, GABAergic interneurons interact with two early transient neuronal populations necessary for correct cortical development, Cajal-Retzius (CR) cells and the subplate (extensively reviewed in reference [16]). CR cells, receive dense GABAergic input [30] and in turn innervate GABAergic cells in early development with GABA receptor signalling a known promoter of apoptosis in CR cells once layer formation is complete around

the second postnatal week [31]. The other early neuronal population, glutamatergic SP neurons, are embedded with neurons that express a range of GABAergic markers [17, 32] and that electrical stimulation and pharmacology experiments suggest provide both tonic and synaptic GABAergic control of SP output [33]. Histological analysis has revealed that the shifting profile of GABAergic SP neurons contain a large number of interneuron subtypes labelled by the 5-HT_3R-GFP transgenic [17] in contrast to adjacent neocortical layer 6. While this could be biased by late born CGE-derived migratory cells, the continued imbalance at later ages suggest that this profile is not transient and more likely due to a unique signalling requirements of SP.

Both CR and SP neurons are fundamental to early circuit formation and set in motion a neonatal time period over which there are significant changes in the nature of activity generated in the emergent layers of neocortex [34-36]. Such activity is characterized by spontaneous synchronized events that propagate through a variety of local and long range circuits across neocortex with the first GABA-dependent events, termed cortical giant depolarising potentials (cGDPs), first apparent midway through the first postnatal week [35]; a time point at which $GABA_A$ receptor antagonists also modulate columnar early gamma oscillations (EGOs) [36]. Evidence from hippocampus suggest that early-born cells from the MGE are critical to GDP generation [37, 38•], but the involvement and contribution of GABAergic interneuron subtypes to neocortical activity has not currently been determined *per se*. Regardless of which subtype it is likely that the complex dynamics of GABA reversal potential, cGDP activity [39] and *in vivo* EGOs [36] provide the ideal environment to promote active synapse formation and consolidation in the neonatal brain [40, 41••].

Parvalbumin-positive basket cells – traditional mediators of neocortical circuit maturation and plasticity

A number of studies have focused on the role of the MGE derived parvalbumin (PV+) basket cells, primarily because these represent the largest group of GABAergic interneuron, are found across all layers of neocortex (Figure 1c), and are readily distinguished in the mature brain by their fast action potentials and basket cell morphologies. These cells undergo two fairly distinct phases of development in neocortex. The second phase, about which most is known, is the classic example of sensory experience-dependent maturation of PV+ cells in visual cortex [42, 43]. This event occurs relatively late in circuit development and in response to multiple checks and balances ranging from control of transcription [44] to GABAergic activity [45-47]. However this is not the onset of PV+ interneuron function in neocortex with this cell type integrating within the first postnatal week into local circuits in visual [48]• and somatosensory

cortex [49]•. This initial phase of synaptic integration appears to be largely governed by molecular cues [50, 51••] and is instructed by afferent PYRs in a class-specific manner [52] including translaminar feed-forward connections [49] at a time when the corresponding pyramidal cell (PYR) – PYR connections are mediated by NMDA receptor 'silent' synapses [53]. The targeting of PV+ interneurons by precise glutamatergic connections suggest that this class play an important role in the emergent circuit, binding together nascent PYR components, even though at this stage they are incapable of sustaining high frequency activity [54]. Moreover it appears that early integration and maturation of PV+ cells reaches a critical threshold to terminate early network activity and initiate the second , sensory experience-dependent phase [51••, 55-57]. This progressive increase in glutamatergic drive is matched by increasing GABAergic control of PV+ cells by other interneuron subtypes (Daniel Lyngholm, SB *unpublished data*), a further level of control that would enable dis-inhibition of PYRs and a window of opportunity for plasticity [58•].

An emergent role for SST+ interneuron subtypes in early circuits.

Somatostatin- (SST+) positive interneuron subtypes have been shown to target PV+ cells in the mature neocortex [59] (Figure 2a). This group of diverse, primarily dendrite-targeting cell originate in the *Nkx2-1*-expressing ventricular zone of the ganglionic eminences early during interneuron neurogenesis. Key determinants of SST+ maturation and glutamatergic afferent input include the activity-dependent transcription factors *Satb1* [60, 61] and *Npas4* [62]•. Evidence from studies in hippocampus, have shown that a number of these early born cells occupy a distinct role in neonatal circuits as Hub cells co-ordinating activity across the neonatal circuit [37, 63]. As such, Hub cells are important for emergent synchrony in the early hippocampus, information flow and ultimately appropriate synaptic integration [64]. In neocortex synaptic integration of SST+ cells occurs early in the first postnatal week and is primarily dominated by local afferent connections irrespective of the layer location [49]. Of note are a population of Martinotti cell, located in infragranular layer 5b, that participate in early feed-forward signalling from the thalamus [65••, 66••] and have been shown to regulate thalamic engagement of PV+ interneurons [65••] and spiny stellate neurons in layer 4 of somatosensory cortex [66••]. These circuits are transient with the L5b-L4 connections coincident with the critical period plasticity in whisker somatosensory cortex [66••](Figure 2b,c). Intriguingly L5b GABAergic cells also innervate somatosensory cortex SP neurons in the first few postnatal days (Daniel Lyngholm, SB *unpublished data*) and develop connections onto layer 2/3 PYRs following the L4 critical period plasticity [49], coincident with the development of L4 to L2/3 circuit maturation [67] and a change in spike timing dependent

plasticity rules in supragranular layers [68]. While SST+ interneurons undoubtedly regulate the timing of emergent activity, it is also apparent that GABA release can control glutamatergic synapse formation at the cellular level [41••, 69]. It is also worth noting in relation to this subtype that perturbing signalling from SST+ cells leads to compensation by other interneurons [66]; data which point to network level control over the amount of GABA signalling in neonatal cortex. Taken together these data suggest that SST+ cells, primarily located in infragranular layers that possess ascending axons that innervate superficial layers are well positioned to initiate and/or influence synaptic plasticity in the developing neocortex.

Synaptic integration of 5 HT_3R interneurons is influenced by neurotransmitter activity

The third major group of GABAergic interneuron are a highly diverse array of subtypes commonly identified by their expression of 5-HT_3R, but that are also recognised by their expression of a wide variety of other markers, notably vasointestinal peptide (VIP), calretinin (CR), reeling (Re) and neuropeptide Y (NPY). The distinct, late origin of these cells in the CGE has made them tractable to a number of genetic/activity manipulation strategies that have resolved subtype-specific rules for the integration of these cells in neocortex [70, 71]. In brief, Re- and CR-positive cells types require normal levels of activity for their migration and integration into the early cortical circuit whereas VIP-positive cells require cell-autonomous expression of the transcription factor *Prox1* to integrate fully into the PYR network. This suggests that the latter are perhaps more hard-wired into the neonatal circuit, in a manner independent of PYR activity. Unsurprisingly, cells from the CGE are susceptible to manipulation of embryonic serotonin levels with Re+ interneurons failing to migrate correctly in the absence of 5-HT_3R [72]. Whereas VIP+ cell migration is disrupted following altered serotonin reuptake [73], albeit that the later manipulation also impacts on thalamic afferent development [74]. Intriguingly, a similar manipulation – dosing with the serotonin reuptake inhibitor fluoxetine – restores plasticity in adult visual cortex via a GABA-dependent mechanism [75].

Are VIP+ interneurons and dis-inhibition of pyramidal cells involved in circuit formation and early plasticity?

Of the various 5-HT_3R subtypes, VIP+ cells have attracted a lot of attention as they are targeted by cross-modal synaptic connections and could promote plasticity via an indirect mechanism,

through their selective inhibition of SST+ cells [59, 76, 77] and resultant disinhibition of PYR cells (Figure 2a); a process that recent evidence suggests is dependent on experience-dependent genetic events [78••], sensory state [79, 80] and the complex interaction between VIP+ and SST+ cells [81]. Evidence for such a mechanism comes from Stryker and colleagues [82••] who demonstrated in a series of short monocular deprivation experiments that activation of VIP+ cells through locomotor activity could potentiate ocular dominance plasticity in binocular V1, and confirmed that this involved specific inhibition of SST+ cells. This avenue for kindling plasticity is distinct from a broader manipulation – transplantation of CGE-derived precursors, which was not able to induce ocular dominance plasticity [83•, 84•] in contrast to MGE grafts [83•, 85]. The inability of CGE transplants to trigger plasticity could arise from reduced integration of transplanted cells into the mature visual circuit [83•] and/or a bias toward Re+ cells in the surviving grafted neurons [84•]. Finally, it is worth noting that both Re + and VIP+ cells also receive thalamic afferent input [28, 86], suggesting a potential role for this cell type in integrating sensory signals from the thalamus in supragranular layers, and thus able to further shape emergent cortical circuits. Given the relatively late integration of these interneurons into the neonatal circuits it is easier to envisage that such role emerges toward the end of the first postnatal week (CV, SJBB, *unpublished data*), after the end of the L4 critical period plasticity in somatosensory cortex.

Early interneuron circuits are distinct from those in the adult

Interneuron circuits change over the course of development to create necessary activity for circuit development and refinement [49•, 65••, 66••, 87]. Unsurprisingly evidence from *in vivo* sensory systems suggest that the function of early GABAergic signalling in cortical processing shifts over development and is distinct from that encountered in adults [88, 89]. However this should not be regarded as a two-stage process – neonate *versus* adult – with GABAergic circuits continuing to alter [90] and change in response to altered sensory input even in the mature brain [91-94]. Moreover, as better genetic tools are developed to parse apart interneuron diversity, it is becoming more and more evident that interneuron subtypes contribute to early circuit maturation and plasticity in a myriad of ways. The transient nature of a number of these early circuits [49•, 65••, 66••] suggest that GABAergic interneuron can act as a scaffold for the acquisition of normal sensory processing (Figure 3). Moreover that there is a carefully choreographed transition in early GABAergic circuits to ensure that information flow through cortical networks is appropriately regulate at each and every stage.

Figure legends

Figure 1. Origin and destination of GABAergic interneurons

(a) Neocortical GABAergic interneuron originate from 2 main proliferative zones: the medial (MGE; *blue*) and caudal ganglionic eminences (CGE, *green*). Interneuron precursors tangentially migrate (*black arrows*) up into the ventral pallium where they integrate with locally-born pyramidal cells (grey triangles). LGE, lateral ganglionic eminence; OB, olfactory bulb. (b) The MGE gives rise to both parvalbumin- (PV+) and somatostatin- (SST+) expressing cells types. The former (*dark blue*) are born throughout the embryonic time window for MGE neurogenesis, whereas SST+ cells (*light blue*) are preferentially born during early time points. The CGE gives rise to the third main group of interneurons – defined by expression of 5-HT_3R (*green*) – these cells are born at later embryonic timepoints. (c) The timing of interneuron subtype neurogenesis reflects the distribution across the depth of the six-layered cortex. Information transfer through the canonical cortical circuit is depicted by the black arrows. The proportion of the 3 main interneuron subtypes for layers 2/3, 4 and 5 are shown to the right [22, 26, 49•]. PV+ cells (dark blue segment) are fairly evenly distributed, while SST+ cells (light blue) are found in deep, infragranular layers. 5-HT_3R+ subtypes (green), including vasointestinal peptide-expressing (VIP+) interneurons are primarily found in greater number in superficial, supragranular layers (layers 2/3). WM, white matter; Th, thalamic afferent input.

Figure 2. Early interneuron circuits can be distinct from those reported in adults

(a) Both main types of MGE-derived interneuron (*blue*) form synaptic connections onto pyramidal cells (PYR; *grey*) with PV+ cells also forming extensive chemical and gap junction coupled networks with other PV+ cells. SST+ cells form synapses onto PV+ cells and also reciprocal connections with VIP+ cells. As such both SST+ and VIP+ cells can disinhibit PYRs (adapted from reference [59]). (b) In neonatal somatosensory cortex L5b SST+ interneurons form a reciprocal synaptic loop with L4 spiny stellate neurons (SSNs; red cell)[66]. This is the main source of inhibition onto SSNs in the absence of mature PV+ input. (c) Following the end of the critical period plasticity the L5b-L4 loop collapses and mature feed-forward inhibition of SSNs emerges [55, 57].

Figure 3. Time line of major circuit events in neonatal mouse somatosensory cortex.

A time line from the day of birth, postnatal day (P)0, until P16. Major window are shown with light grey bars, network events with medium grey and interneuron integration and circuits shown with dark grey. CPP, critical period plasticity; Th, thalamus; L4, layer 4; L2/3, layer 2/3. cENO, cortical early network oscillation [35]; cGDP, cortical giant depolarising potential; EGOs, early gamma oscillations [36].

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Figure 1

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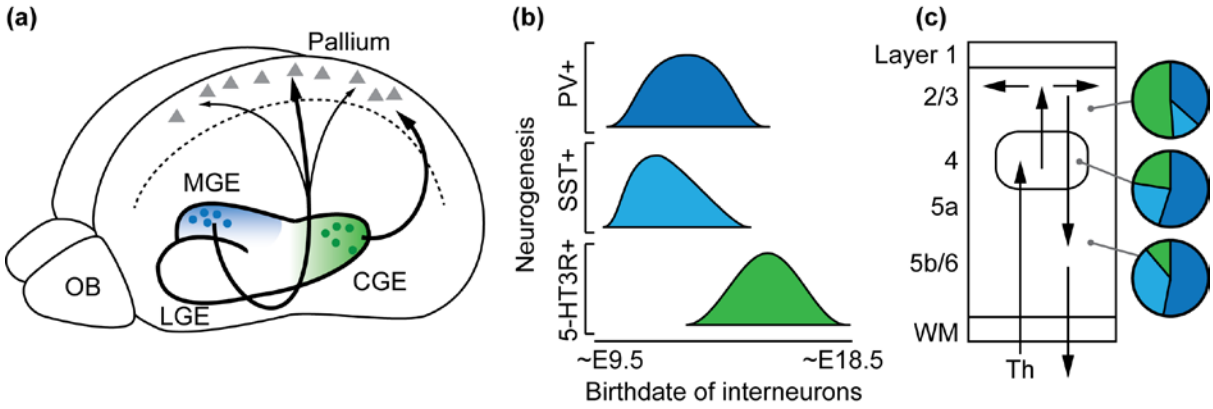

Figure 2

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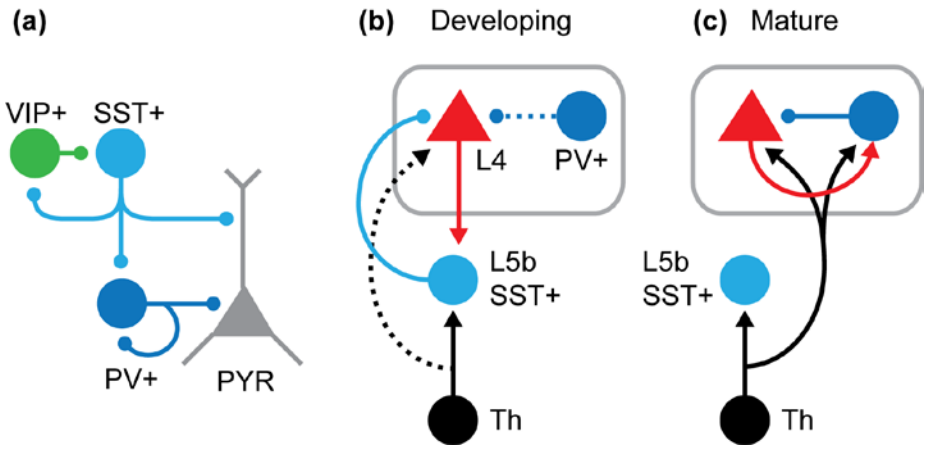

Figure 3

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