Neuroscience and Biobehavioral Reviews 124 (2021) 179–192

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

The postnatal GABA shift: A developmental perspective

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ARTICLE INFO

Keywords:
GABA
GABA polarity
Chloride
Chloride cotransporters
KCC2
NKCC1
Molecular mechanisms
Circuit formation
Brain development
Autism
Neurodevelopmental disorders

ABSTRACT

GABA is the major inhibitory neurotransmitter that counterbalances excitation in the mature brain. The inhibitory action of GABA relies on the inflow of chloride ions (Cl^-), which hyperpolarizes the neuron. In early development, GABA signaling induces outward Cl^- currents and is depolarizing. The postnatal shift from depolarizing to hyperpolarizing GABA is a pivotal event in brain development and its timing affects brain function throughout life. Altered timing of the postnatal GABA shift is associated with several neurodevelopmental disorders. Here, we argue that the postnatal shift from depolarizing to hyperpolarizing GABA represents the final shift in a sequence of GABA shifts, regulating proliferation, migration, differentiation, and finally plasticity of developing neurons. Each developmental GABA shift ensures that the instructive role of GABA matches the circumstances of the developing network.

Sensory input may be a crucial factor in determining proper timing of the postnatal GABA shift. A developmental perspective is necessary to interpret the full consequences of a mismatch between connectivity, activity and GABA signaling during brain development.

1. Introduction

The direction of γ-aminobutyric acid (GABA) currents through ionotropic GABA receptors reverses during brain development from depolarizing to hyperpolarizing. This developmental change is often referred to as the postnatal GABA shift, and is caused by a change in the expression of the two major chloride (Cl^-) transporters, Na-K-2Cl cotransporter isoform 1 (NKCC1) and the K-Cl cotransporter isoform 2 (KCC2) (Fig. 1). Conservation of the GABA shift across brain structures and species, including frogs, turtles, mice, rats, rabbits, birds, and most likely also humans, suggests that the GABA shift has been preserved during evolution and is essential for brain development (Ben-Ari et al., 2007; Tang, 2020).

Defects in the GABA shift are associated with a wide variety of neurodevelopmental disorders, including autism (Schulte et al., 2018). Recent experimental studies have suggested postnatal GABA signaling as an interesting common therapeutic target for neurodevelopmental disorders. In animal models of Fragile X (He et al., 2019), Down syndrome (Deidda et al., 2015b) and Rett syndrome (Banerjee et al., 2016), restoring inhibitory GABA signaling during a restricted postnatal period yielded significant improvements in brain function. Pilot studies in human patients (Bruining et al., 2015; Lemonnier et al., 2017) have also been encouraging. These promising findings are raising renewed attention to the central role for GABA signaling in brain development. Why is the postnatal GABA shift so important and when exactly does GABA need to shift? To answer these questions we first examine the role of depolarizing GABA in the developing hippocampus and cortex. Consecutively, depolarizing GABA instructs proliferation, migration and differentiation of immature neurons during early neuronal development. In addition, depolarizing GABA can contribute to spontaneous activity in some brain areas. We conclude that the postnatal GABA shift represents one of a series of developmental shifts in the roles of GABA during brain development. In the second part of the review, we focus on the postnatal shift to hyperpolarizing GABA, which is required at later stages to regulate activity and to tighten plasticity rules to optimize neuronal networks to process (sensory) information throughout life. We discuss how sensory drive may be a crucial factor in determining proper timing of the postnatal GABA shift and how a developmental perspective will help to interpret the consequences of a mismatch between connectivity, activity and GABA signaling during brain development.

2. Depolarizing GABA mediates early neuronal development

GABA signaling is present already early in development, long before neurons form networks via synapses. For instance, embryonic and neuronal crest stem cells release and respond to GABA via $GABA_A$

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https://doi.org/10.1016/j.neubiorev.2021.01.024
Received 23 September 2020; Received in revised form 13 January 2021; Accepted 28 January 2021
Available online 4 February 2021
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receptors in an autocrine way (Andäng et al., 2008; Wang and Kriegstein, 2008a). In the following sections, we will describe the multiple roles of GABA in brain development in rodents (mostly mice). When other model organisms were used, we will state them explicitly. From around mouse embryonic day (E)9, GABA is released from growth cones of interneurons (Gao and van den Pol, 2000; Taylor and Gordon-Weeks, 1991). The earliest depolarizing GABAergic synaptic responses are measured approximately one week later (at E16-20) in the cortical plate (CP) and hippocampus, when the first GABAergic synapses emerge (Demarque et al., 2002; Gozlan and Ben-Ari, 2003; LoTurco et al., 1995; Owens et al., 1999, 1996). As GABA is depolarizing at this stage, GABA signaling can activate voltage-gated calcium (Ca^{2+}) channels (Furukawa et al., 2017; Kirmse et al., 2015, 2010; LoTurco et al., 1995; Owens et al., 1996; Tyzio et al., 2014). As we will describe below, depolarizing GABA and GABA-induced Ca^{2+} influx are important instruction signals to regulate development of the embryonic brain (Fig. 2). Rather than simply promoting developmental processes in young neurons, GABA governs developmental switching points, from proliferation to migration, from migration to differentiation, and finally from differentiation to synapse formation. Thus, while being depolarizing, GABA's instructive role shifts in each step of early network development.

2.1. Depolarizing GABA mediates proliferation

An important role for GABA in early development is to mediate cell cycle progression of stem cells in the developing brain (Fig. 2B). Neurons are generated within the developing cortex from neural stem cells. The primary neural stem cells, the radial glia cells, are located in the ventricular zone (VZ), while the subventricular zone (SVZ) is a secondary proliferative region where intermediate progenitor cells reside. Whereas depolarizing GABA promotes proliferation of primary stem cells in the VZ (Haydar et al., 2000; Young et al., 2012), GABA signaling actually inhibits the proliferation of intermediate precursors in the SVZ (Haydar et al., 2000). The negative effect in SVZ seems stronger, which explains the observed decrease in progenitor proliferation in slices containing both regions after depolarization with GABA or high extracellular potassium (K^+) (Haydar et al., 2000; Liu et al., 2005; LoTurco et al., 1995). GABA has been shown to inhibit cell cycle progression by mediating the expression levels of different cell cycle regulators in a wide variety of neurons, both *in vitro* and *in vivo* (Andäng et al., 2008; Cesetti et al., 2011; Duveau et al., 2011; Fernando et al., 2011; Nguyen et al., 2003; Song et al., 2012). However, the precise molecular pathways used by GABA to promote proliferation in VZ and inhibit proliferation in the SVZ remain to be elucidated.

2.2. Depolarizing GABA mediates migration

Newborn neurons migrate away from the VZ and SVZ through the intermediate zone (IZ) to the developing CP. This migration is regulated by depolarizing GABA (reviewed by (Luhmann et al., 2015)) (Fig. 2C). Depolarization, either by GABA or via high extracellular K^+, promotes migration of dissociated embryonic cortical neurons in chemotaxis chambers (Behar et al., 1998, 1996) whereas interference with GABAergic depolarization reduces migration of cortical neurons *in vivo* (Inoue et al., 2012). Evidence from embryonic cortical slice cultures shows that depolarizing GABA promotes migration from VZ via $GABA_A$-ρ receptors (Behar et al., 2000; Denter et al., 2010). $GABA_A$-ρ receptors are ionotropic receptors that produce slow, but large and sustained Cl^- currents when activated (Woodward et al., 1993). $GABA_A$-ρ receptors are only transiently expressed by migrating neurons and replaced by more conventional $GABA_A$ receptors once neurons reach the CP (Denter et al., 2010). Inhibiting conventional $GABA_A$ receptors with bicuculline, which does not block $GABA_A$-ρ receptors (Woodward et al., 1993), actually increases the number of neurons reaching the CP (Behar et al., 2000; Bolteus, 2004; Denter et al., 2010; Heck et al., 2007), suggesting that $GABA_A$ receptor signaling inhibits the migration of neurons once $GABA_A$-ρ receptors are downregulated. GABA also limits migration in the olfactory bulb and in newborn granule cells in the adult hippocampus (Duveau et al., 2011; Fueshko et al., 1998).

GABAergic interneurons are generated in the ganglionic eminences of the ventral telencephalon and follow a tangential migration route into the developing cortex and hippocampus between approximately E10 and E16 (Hu et al., 2017b). Depolarizing GABA promotes the tangential migration of interneurons (Fig. 2A) (Bortone and Polleux, 2009; Inada et al., 2011). Once interneurons start expressing KCC2 and GABAs effect becomes hyperpolarizing, Ca^{2+} signaling decreases and migration slows down (Bortone and Polleux, 2009). $GABA_A$-ρ receptors are also expressed in GABAergic interneurons (Martinez-Delgado et al., 2010; Semyanov and Kullmann, 2002), but their role in interneuron migration has not been explored.

2.3. Depolarizing GABA promotes neurite growth and synapse formation

After young pyramidal neurons have reached their final destination, depolarizing GABA-induced Ca^{2+} influx promotes outgrowth of neurites (reviewed by (Sernagor et al., 2010)) (Fig. 2D) in cultures

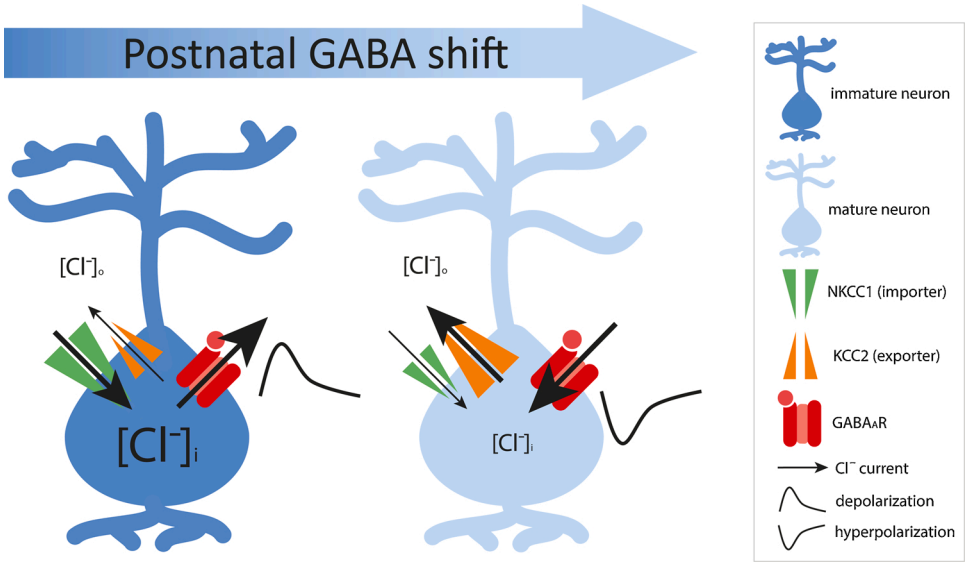

Fig. 1. The postnatal GABA shift is due to a decrease in intracellular chloride (Cl^-) concentration.
The direction of the flow of Cl^- ions through $GABA_A$ receptors depends on the electrochemical Cl^- gradient. Left: In the immature brain, the intracellular Cl^- concentration is relatively high, as Cl^- transport over the membrane is dominated by NKCC1. Activation of $GABA_A$ receptors results in an outflow of Cl^- resulting in membrane depolarization. Right: During development, intracellular Cl^- levels decrease, due to increased expression and activity of KCC2. As a result, activation of $GABA_A$ receptors leads to an entry of Cl^- and GABAergic signaling results in hyperpolarization of mature neurons.

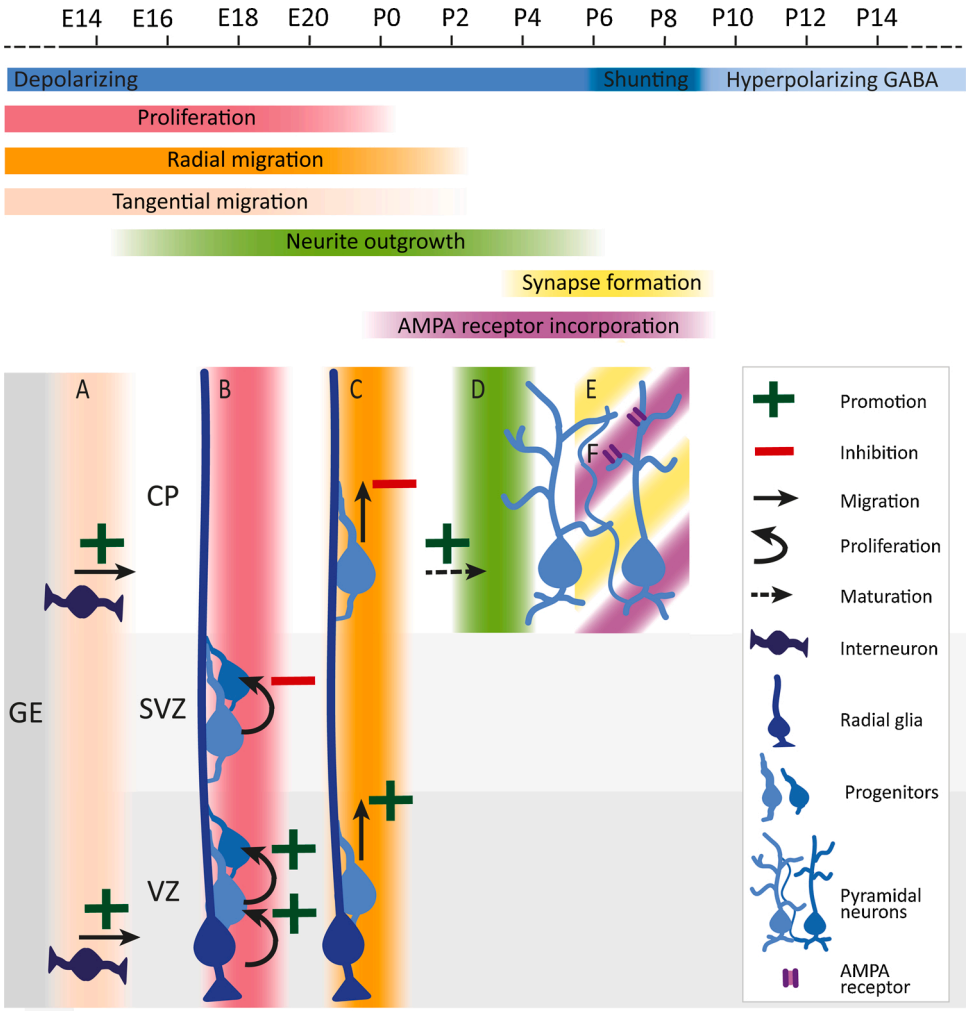

Fig. 2. Developmental switching points, instructed by GABA signaling.
Depolarizing GABA guides the construction of the brain early in development by mediating the migration, proliferation and maturation of synapses of neuronal precursors and interneurons in the developing cortex. GE = ganglionic eminence, CP = cortical plate, SVZ = subventricular zone, VZ = ventricular zone.

(Ageta-Ishihara et al., 2009; Barbin et al., 1993; Gascon et al., 2006; Maric et al., 2001; Nakajima and Marunaka, 2016; Reynolds et al., 2008) and *in vivo* (Cancedda et al., 2007; Wang and Kriegstein, 2011, 2008b; Young et al., 2012). GABA also promotes dendritic arborization in newborn neurons in the adult hippocampus and olfactory bulb (Duveau et al., 2011; Ge et al., 2006; Gascon et al., 2006). In addition, GABA promotes the formation of synapses (Fig. 2E). Blockade of GABAergic transmission with bicuculine for 24 h in cultured intact hippocampi prevented the developmental increase in the frequency of inhibitory synaptic currents that normally occurs after birth (Colin-Le Brun et al., 2004). In addition, local depolarizing GABA signaling can induce the formation of excitatory and inhibitory synapses on young dendrites (Oh et al., 2016). Depolarizing GABA also promotes synapse formation onto newborn neurons in the dentate gyrus of adult mice (Ge, 2006).

GABA-induced postsynaptic depolarization can trigger activity-dependent structural plasticity and neurite growth via Ca^{2+} influx (Oh et al., 2016; Sernagor et al., 2010), implying GABA is merely used as a source of depolarization. However, specific and Ca^{2+} independent GABA signaling was also recently reported. Depolarizing GABA was found to induce intracellular Mg^{2+} release from mitochondria to promote neuronal maturation (Yamanaka et al., 2018). In addition, mitochondrial activity can result in sequestration of GABA within mitochondria in flies, possibly limiting excessive GABAergic signaling (Kanellopoulos et al., 2020). Future studies should further explore this intriguing link between mitochondrial and GABA signaling in the developing brain.

2.4. *Depolarizing GABA promotes synapse maturation*

Glutamatergic synapses in the early postnatal brain often lack AMPA-type glutamate receptors. Synapses that only contain NMDA receptors, which are blocked by Mg^{2+} at negative membrane potentials, are often called 'silent' synapses (Wang and Kriegstein, 2009). Glutamatergic synapses can be 'unsilenced' by insertion of AMPA receptors after NMDA receptor activation. GABAergic depolarization removes the Mg^{2+} block, thereby facilitating unsilencing of immature glutamatergic synapses of rodents and Xenopus (Akerman and Cline, 2006; Chancey et al., 2013; Leinekugel et al., 1997; van Rheede et al., 2015). The AMPA/NMDA receptor ratio increases drastically after birth until around postnatal day (P)10 in rodents (Durand et al., 1996; Isaac et al., 1997; Itami et al., 2003; Rumpel et al., 1998) and between stage 40 and 49 in Xenopus tadpoles (Akerman and Cline, 2006; van Rheede et al., 2015; Wu et al., 1996), which corresponds with the period just before GABA becomes hyperpolarizing (Fig. 2F). The frequency of spontaneous glutamatergic currents increases substantially during this period, probably reflecting a combination of an increased number of glutamatergic synapses and increased insertion of AMPA receptors in rodents and Xenopus (Akerman and Cline, 2006; Durand et al., 1996; Isaac et al., 1997; van Rheede et al., 2015; Wu et al., 1996). When postnatal GABA depolarization is chronically impaired, AMPA-mediated synaptic currents eventually develop normally (Chudotvorova et al., 2005; Ge et al., 2006; Nakanishi et al., 2007; Pfeffer et al., 2009; Wang and Kriegstein,

2011, 2008b), suggesting that other factors besides GABA can provide the required depolarization to promote glutamatergic synapse formation.

In summary, GABA plays pivotal roles in the initial formation of neuronal networks in the embryonic and early postnatal brain. Depolarizing GABA provides the Ca^{2+} influx to mediate the initial steps of network construction at a time when glutamatergic signaling is still scarce. GABA signaling also provides more specific instructions. Depolarization by GABA or high K^+ promotes the proliferation of early neuronal precursors, but concomitantly limits proliferation at later stages. In a similar dichotomic fashion, GABA and high K^+ promote migration of newborn neurons, but limit migration of older neurons. In addition, depolarization by GABA promotes the integration of young neurons into networks along with their maturation, possibly not only through Ca^{2+}, but also Mg^{2+} signaling. Thus, developing neurons use GABA as an instructive signal to accomplish a sequence of developmental processes. The instruction given by GABA depends on the intrinsic properties of the developing neurons, such as the expression of specific receptors and Cl^- transporters, which change as the neurons mature. Currently, only a few of these cell-intrinsic factors are known (e.g. the transient expression of $GABA_A$-ρ receptors in migrating neurons). In addition, local cues may modulate the GABAergic instruction signal or indirectly affect intrinsic properties of the neurons in a region-specific manner. It will be important for future research to identify the precise molecular factors and mechanisms that enable a relatively constant GABA signal to trigger a specific sequence of developmental processes in young neurons.

3. Roles of GABA in early activity

The contribution of depolarizing GABA to neuronal activity is rather complex. It is important to realize that GABA-induced depolarization and Ca^{2+} influx do not necessarily go hand in hand with neuronal excitation as the opening of $GABA_A$ receptors inevitably results in an increase in membrane conductance: the membrane becomes 'leaky'. This means that glutamate-induced depolarizations are attenuated when traveling from the dendrite to the soma, which is generally referred to as 'shunting'. Shunting reduces overall excitation, regardless of the direction of Cl^- flux through the $GABA_A$ receptors. Depolarizing GABA will be excitatory or shunting depending on the exact interplay between Cl^- levels, activity levels and the number of excitatory and inhibitory synapses onto developing neurons (Gao et al., 1998; Le Magueresse and Monyer, 2013; Morita et al., 2006; Staley and Mody, 1992). This complex interplay likely explains the discrepancies in GABAs actions found in slices versus *in vivo* and differences between brain regions.

There is ample evidence for GABA-induced excitation in brain slices. Application of GABA induces firing and increases excitatory postsynaptic current (EPSC) frequency in E18-P13 neocortical and hippocampal slices (Gozlan and Ben-Ari, 2003; Khazipov et al., 2004; Kirmse et al., 2010; Owens et al., 1996; Rheims et al., 2008) and optogenetic activation of GABAergic interneurons increases EPSC frequency in hippocampal and cortical slices from P2–9 mice (Valeeva et al., 2016). Thus, in brain slices of newborn rodents GABA-induced depolarization is sufficient to induce action potential firing and GABA can be truly excitatory.

Excitatory GABA can also support spontaneous oscillations in immature brain slices. During the first days after birth spontaneous oscillations are characterized by giant depolarizing potentials (GDPs) (Blankenship and Feller, 2010). Hippocampal GDPs increase when GABAergic depolarization is enhanced (Spoljaric et al., 2019). In contrast, hippocampal and cortical GDPs transform into epileptiform discharges after loss of depolarizing GABA (Allène et al., 2008; Ben-Ari et al., 1989; Dzhala et al., 2005; Khalilov et al., 2015, 1997; Leinekugel et al., 1997; Mohajerani and Cherubini, 2005; Pfeffer et al., 2009; Rheims et al., 2008; Sipila et al., 2006; Valeeva et al., 2010; Wells et al., 2000). This is because the action of GABA changes from depolarizing to hyperpolarizing during a GDP cycle due to the large reduction in intracellular Cl^- concentration when many $GABA_A$ channels open. GDPs are therefore driven, but at the same time also limited by, GABA signaling (Khalilov et al., 2015; Lombardi et al., 2018). Around P8-10 the frequency of GDPs starts to decrease, until GDPs fully disappear after P12 (Ben-Ari et al., 1989; Khazipov et al., 2004; Rheims et al., 2008). Around the same time, GABA shifts from being mainly excitatory to being shunting during baseline activity in these slices (Salmon et al., 2020; Valeeva et al., 2016).

In the first weeks after birth, activity in the hippocampus of living rodent pups is characterized by sharp waves (SWs) during rest, the *in vivo* counterpart of GDPs in hippocampal slices (Leinekugel et al., 2002). Chemogenetic suppression of GABAergic interneurons in the hippocampus of P3 mice decreases SW frequency and amplitude (Murata and Colonnese, 2020). Moreover, SWs are acutely blocked when GABA-induced depolarization is abolished (Sipila et al., 2006). This clearly demonstrates that depolarizing GABA contributes to spontaneous postnatal hippocampal activity *in vivo*. The shift to inhibitory GABA in the hippocampus occurs around P7 (Murata and Colonnese, 2020).

The situation in the postnatal cortex seems different. Release of GABA in the cortex of anaesthetized mice at P3–7 induces Ca^{2+} influx, but decreases neuronal firing (Che et al., 2018; Kirmse et al., 2015; Murata and Colonnese, 2020; Valeeva et al., 2016). These observations suggest that in the postnatal cortex GABA is depolarizing, but acts mostly inhibitory via shunting. This is consistent with studies showing that depolarizing GABA is not involved in early oscillations in the newborn cortex *in vivo* (Kirmse et al., 2015; Marguet et al., 2015; Minlebaev et al., 2011, 2006). These cortical oscillations depend strongly on AMPA receptor activation and are modulated by cholinergic activity (Yang et al., 2016).

So whereas GABA-induced depolarization and Ca^{2+} influx promote network formation on a cellular level across the brain, their precise impact on network activity is highly dependent on both Cl^- levels and locally ongoing activity. The combination of glutamatergic, GABAergic and other inputs determine the distribution and conductance of ions across the neuronal membrane and thereby the impact of GABAergic signaling. As a result, the shift from depolarizing to hyperpolarizing GABA signaling is not simply accompanied by a shift from GABAergic excitation to inhibition. Depolarization by GABA can induce action potentials when activity is relatively low, for instance in brain slices. In the intact brain, regional heterogeneity is important. GABA can induce firing and amplify spontaneous activity in the perinatal hippocampus. With the increase in hippocampal activity levels and decrease in Cl- levels during the second postnatal week, inhibitory actions of GABA are assured. In the newborn cortex, depolarizing GABA is mostly shunting and therefore inhibitory.

4. Hyperpolarizing GABA: development of input sensitivity

In the first weeks after birth, spontaneous activity in the sensory cortex of rodents decreases and the network becomes more susceptible to sensory input. The shift to hyperpolarizing GABA is tightly coupled to the recruitment of interneurons by thalamocortical input. In P3-5 slices, when GABA is still depolarizing, GABAergic cells in layer IV of barrel cortex are hardly engaged by thalamocortical input. Only by P7 thalamocortical input activates feedforward GABAergic transmission, which is then hyperpolarizing (Daw et al., 2007). Without thalamic input, for instance after subplate ablation in cats, the shift to hyperpolarizing GABA does not occur (Kanold and Shatz, 2006). In this way, hyperpolarizing GABAergic responses are assured when the cortex becomes receptive to sensory input and spontaneous activity decreases (Lohmann and Kessels, 2014; Toyoizumi et al., 2013). With increasing sensory input, hyperpolarizing GABA becomes essential to enhance sensory sensitivity, improve temporal precision, sharpen the tuning to sensory stimuli (Pouille and Scanziani, 2001; Wehr and Zador, 2003) and to

sharpen the coincidence window for plasticity in the developing network (Kanold and Shatz, 2006; Pan-Vazquez et al., 2020). The GABA shift also makes GABAergic signaling faster. During development, $GABA_A$ receptor α3 subunits are replaced by the faster α1 subunits, resulting in a faster decay of GABAergic synaptic currents (Laurie et al., 1992; Taketo and Yoshioka, 2000). This change in subunit composition depends on the developmental decrease in the Cl^- concentration, independently of $GABA_A$ receptor signaling (Kanold and Shatz, 2006; Succol et al., 2012).

Together, these studies suggest that GABAergic interneurons become engaged by thalamocortical input in the cortex around the time when GABA shifts. The shift to hyperpolarizing GABA increases input sensitivity of the network and short hyperpolarizing GABAergic responses tighten plasticity rules and improve temporal precision. The shift from depolarizing to hyperpolarizing GABA signaling seems therefore tightly linked to the connectivity and activity in the local network, and the shift may be closely aligned to the period when circuits are shaped by external (sensory) inputs. In the second part of this review we will discuss the regulators of the timing of the postnatal GABA shift as well as the consequences for synaptic development when the timing is off.

5. Timing of the postnatal GABA shift

The postnatal decrease in Cl^- concentration has been measured using fluorescent Cl^- indicators and by determining the driving force for GABAergic transmission using cell attached or perforated patch recordings. The average Cl^- driving force shifts from positive to negative around P10-14 in pyramidal neurons of hippocampal and cortical slices (Kirmse et al., 2015; Pisella et al., 2019; Rivera et al., 1999; Romo-Parra et al., 2008; Stein et al., 2004; Sulis Sato et al., 2017; Tyzio et al., 2007). Interestingly, *in vivo* Cl^- levels decrease approximately 4 days earlier in the cortex than in the hippocampus (Murata and Colonnese, 2020). Moreover, Cl^- levels decrease approximately a week earlier in GABAergic cells compared to pyramidal cells (Banke and McBain, 2006; Bortone and Polleux, 2009), although hippocampal PV cells seem to synchronize with pyramidal neurons (Sauer and Bartos, 2010). In female hippocampal and midbrain slices the GABA shift is several days earlier compared to males (approximately P6-10 in females and P14-17 in males) (Galanopoulou, 2008; Kyrozis et al., 2006; Nuñez and McCarthy, 2007), while the GABA shift in the cerebellum is actually advanced in males by 4 days (Roux et al., 2018). Thus the timing of the GABA shift appears strongly dependent on cell type, sex and brain region. It should also be noted, that the variance in intracellular Cl^- concentration found between individual neurons is large (Galanopoulou, 2008; He et al., 2014; Kyrozis et al., 2006), both *in vivo* and *in vitro* and across methods used to measure Cl^- levels (Galanopoulou, 2006; He et al., 2014; Kirmse et al., 2015; Owens et al., 1996; Pisella et al., 2019; Rivera et al., 1999; Romo-Parra et al., 2008; Stein et al., 2004; Sulis Sato et al., 2017; Yamada et al., 2004) and that the Cl^- concentration in individual neurons also varies over time and is dependent on activity in the network (Khalilov et al., 2015; Lombardi et al., 2018). The Cl^- concentration is even non-uniformly distributed within a single pyramidal neuron and GABAergic reversal potentials become progressively more negative from the Axon Initial Segment (AIS) to the soma, but less negative from the soma into the dendrites (Khirug, 2012; Pan-Vazquez et al., 2020; Rinetti-Vargas et al., 2017; Romo-Parra et al., 2008). This illustrates that the postnatal GABA shift is not a simple switch that takes place at a certain moment in postnatal development, but rather reflects a gradual change in neuronal Cl^- homeostasis, such that GABA signaling gradually becomes more hyperpolarizing within local neuronal networks.

5.1. Developmental expression pattern of chloride transporters

The developmental decrease in intracellular Cl^- concentration is established by an increase in the relative expression and activity of postnatal chloride exporter KCC2 compared to importer NKCC1 (Fig. 1) in both excitatory and inhibitory neurons (Gulyás et al., 2001; Otsu et al., 2020; Rivera et al., 1999; Sauer and Bartos, 2010; Yamada et al., 2004). The effect of NKCC1 inhibitor bumetanide on the GABAergic driving force decreases with development in excitatory neurons, indicating that the relative contribution of NKCC1 to GABA function decreases (Banke and McBain, 2006). It remains unresolved if the decrease in NKCC1 function reflects a decrease in its expression. While some studies report a developmental downregulation of NKCC1 mRNA and protein levels over the first postnatal weeks (Dzhala et al., 2005; Shimizu-okabe et al., 2002; Yamada et al., 2004), others have reported that NKCC1 levels actually increase over development (Clayton et al., 1998; Sun and Murali, 1999; Yan et al., 2001). The discrepancy may be explained by differences in probe sequences and antibodies used for detection of NKCC1, which may result in different sensitivity for the two main NKCC1 isoforms (NKCC1a and b). Inclusion of male and female animals might aggravate discrepancies in NKCC1 expression patterns, as levels of NKCC1 are elevated in embryonic and newborn male hippocampi and midbrains compared to females (Damborsky and Winzer-serhan, 2012; Murguía-Castillo et al., 2013). Inclusion of glia in the samples may also contribute, as NKCC1 mRNA is also present in astrocytes (Yan et al., 2001).

KCC2 is exclusively expressed by neurons and not by glia (Payne et al., 1996). KCC2s mRNA and protein levels increase during postnatal rodent development (Dzhala et al., 2005; Kovács et al., 2014; Lee et al., 2010; Lu et al., 1999; Rivera et al., 1999; Shimizu-okabe et al., 2002; Stein et al., 2004). This is due to an increase in expression of KCC2b levels, while KCC2a levels remain constant (Uvarov et al., 2007). Total KCC2 expression levels are increased in early postnatal interneurons versus pyramidal neurons (Bortone and Polleux, 2009) and in female compared to male brains (Kang et al., 2015; Murguía-Castillo et al., 2013). Posttranslational modifications further contribute to the developmental increase in KCC2 function (Schulte et al., 2018). For instance, KCC2 becomes dephosphorylated at threonine residues T906 and T1007 (Friedel et al., 2015; Kahle et al., 2013; Moore et al., 2019; Pisella et al., 2019; Rinehart et al., 2009), while it gets phosphorylated at serine residue S940 (Kahle et al., 2013; Lee et al., 2007; Moore et al., 2019) during postnatal development. These modifications enhance KCC2 function and membrane stability.

5.2. KCC2: more than a chloride transporter

The postnatal upregulation of KCC2 serves other roles in brain development than inducing low internal Cl^- levels. In mature neurons, KCC2 proteins are enriched near synapses (Báldi et al., 2010; Chamma et al., 2013; Gulyás et al., 2001; Kovács et al., 2014). KCC2 resides in a multi-protein complex in the neuronal membrane, and is coupled to numerous other proteins, including ion channels, neurotransmitter receptors (Garand et al., 2019; Huang et al., 2012; Wright et al., 2017), cytoskeleton associated proteins and various enzymes (Blaesse and Schmidt, 2015; Smalley et al., 2020b). The developmental increase in KCC2 levels therefore supports neuronal maturation via various structural roles, independent of Cl^- transport. For instance, KCC2 indirectly contributes to the hyperpolarization of the resting membrane potential in developing neurons by stabilizing Task-3 potassium channels in the neuronal membrane (Goutierre et al., 2019). In addition, KCC2 facilitates activity-induced spine growth via interactions with the actin cytoskeleton. KCC2 promotes actin dynamics in spines and supports AMPA receptor insertion and confinement (Chevy et al., 2015; Gauvain et al., 2011). Importantly, all of these roles where shown to be independent of the KCC2 function in transporting Cl^-, but rely on the structural interaction of KCC2 with other proteins. Interestingly, the structural function of KCC2 and its role in Cl^- transport sometimes have opposite effects. For instance, KCC2 overexpression in the developing cortex leads to an increase in spine density, via its interaction with actin (Awad et al., 2018; Fiumelli et al., 2013; Puskarjov et al., 2017). However, the KCC2-induced increase in spine density is prevented by

boosting the Cl^- transport function of the overexpressed KCC2, presumably because spine growth is counteracted by an increase in GABAergic inhibition in the network (Awad et al., 2018).

6. What triggers the postnatal GABA shift?

An important open question is how the shift from NKCC1 to KCC2 dominated Cl^- transport is triggered in developing neurons (Medina et al., 2014). As the shift also occurs in neuronal cultures and organotypic slices (Dumon et al., 2018; Ganguly et al., 2001; Kelsch et al., 2001; Khirug et al., 2005; Ludwig et al., 2011b, 2011a; Perrot-Sinal et al., 2001; Rivera et al., 1999; Sun et al., 2013; Titz et al., 2003), the GABA shift is (at least partly) induced by an intrinsic developmental program.

6.1. Molecular factors regulating the GABA shift

One intriguing study has suggested that neuroligin-2 (NL2) plays a key role in triggering the GABA shift. NL2 is a postsynaptic cell adhesion molecule specific for GABAergic synapses (Blundell et al., 2009). Expression of NL2 increases during postnatal cortical development. Interestingly, the increase in NL2 expression was found to precede the increase in KCC2 expression and NL2 levels directly influence KCC2 expression, independent of network activity. Knockdown of NL2 decreases KCC2 expression and results in GABAergic depolarization, even in mature cortical neurons (Sun et al., 2013). This strongly suggests that NL2 directly regulates KCC2 expression and is required for the maintenance of KCC2 function and GABAergic inhibition (Blundell et al., 2009). The mechanism via which NL2 enhances KCC2 function and the trigger for the developmental increase in NL2 levels have not been resolved.

In addition to NL2, many factors have been identified that do not directly regulate KCC2 expression, but that are able to promote or repress the postnatal GABA shift. Leptin, estradiol and Brain-Derived Neurotrophic Factor (BDNF) precursor pro-BDNF inhibit KCC2 function and may thereby repress a precocious GABA shift. Leptin is a hormone that regulates energy levels and immune responses in the mature brain, but functions as a neurotrophic signal during brain development (Dumon et al., 2018). Plasma leptin levels decrease during the second postnatal week when GABA becomes hyperpolarizing. Leptin weakens expression of KCC2 and its stability in the plasma membrane (Dumon et al., 2018). Estradiol is a testosterone derivative. Its levels decrease gradually in the first two weeks after birth of male and female rats (Konkle and McCarthy, 2011). Estradiol acutely increases NKCC1 function and decreases KCC2 expression in slices (Galanopoulou and Moshé, 2003; Nakamura et al., 2004; Perrot-Sinal et al., 2001; Perrot-Sinal et al., 2007). In the mature brain BDNF promotes neuronal survival and outgrowth (Ghosh et al., 1994). However, in the first postnatal week, its precursor protein pro-BDNF, which exhibits proapoptotic functions, constitutes the main isoform in the brain (Menshanov et al., 2015; Yang et al., 2009). In utero electroporation of a cleavage-resistant pro-BDNF, which cannot be processed into BNDF, decreased KCC2 expression and kept GABA depolarizing in the cortex (Riffault et al., 2018). Together, these results suggest that abundance of leptin, estradiol and pro-BDNF during the first postnatal week helps to keep KCC2 expression low.

In sharp contrast with its precursor, mature BDNF promotes KCC2 function in young neurons via neurotrophin/tropomyosin kinase B (TrkB) receptors (Carmona et al., 2006). Treatment with BDNF increases KCC2 levels (Ludwig et al., 2011b) and KCC2 levels are increased in BDNF-overexpressing mice (Aguado et al., 2003). However, KCC2 function is not affected in BDNF knockout (KO) mice (Puskarjov et al., 2015), indicating that BDNF can accelerate the GABA shift, but that its presence is not absolutely required. Together, these findings suggest that the postnatal shift from pro-BDNF to BDNF regulates the timing of the GABA shift by releasing the negative control by pro-BDNF and by actively promoting KCC2 expression via TrkB receptors.

Other factors that have been shown to actively promote the GABA shift by increasing KCC2 function include neurturin (Ludwig et al., 2011a), TGFβ2 (Roussa et al., 2016), sonic hedgehog receptor Smo (Delmotte et al., 2019), nicotine (Damborsky and Winzer-serhan, 2012; Liu et al., 2006), IGF1 (Baroncelli et al., 2017; Kelsch et al., 2001), allopregnanolone (Mòdol et al., 2014), thyroid hormone (Friauf et al., 2008; Sawano et al., 2013), testosterone and its derivative dihydrotestosterone (Galanopoulou and Moshé, 2003) and oxytocin (Leonzino et al., 2016). Many of these factors likely cooperate to promote KCC2 function and the postnatal GABA shift. For instance, upregulation of KCC2 by neurturin and BDNF is mediated by activation of a common pathway involving ERK1/2 and the transcription factor Egr4 (Ludwig et al., 2011a, 2011b) and activation of nicotinic acetylcholine receptors, Smo, IGF1 receptors and thyroid hormone receptors increase BDNF levels (Carro et al., 2000; Damborsky and Winzer-serhan, 2012; Landi et al., 2009; Radzikinas et al., 2011; Shulga et al., 2009).

In conclusion, the timing of the GABA shift is tightly regulated in the developing brain through external and internal factors, as well as hormones. Specific factors prevent GABA from shifting too early, while other factors assure the postnatal GABA shift is not too late.

6.2. Spontaneous and externally-driven neuronal activity promote the GABA shift

Even before sensory input drives neuronal activity, the developing brain displays various forms of spontaneous activity, as mentioned above. Many of the factors that promote the postnatal GABA shift are activity-dependent, including BDNF and IGF1 (Cao et al., 2011; Porcher et al., 2011). This means that the timing of the GABA shift is coordinated with early network activity. For instance, disruption of spontaneously generated activity in the cochlea prior to the onset of auditory input results in decreased KCC2 function and prevents the GABA shift in newborn animals (Kotak and Sanes, 1996; Shibata et al., 2004; Vale et al., 2003; Vale and Sanes, 2000).

Cortical BDNF and IGF1 levels increase via sensory input (Castren et al., 1992; Landi et al., 2009; Tropea et al., 2006) and GABAergic maturation is strongly influenced by early life experience. For instance, prenatal maternal restraint stress as well as repeated separations of newborn pups from their mother induce a delay in the GABA shift of newborn mice (Furukawa et al., 2017; Hu et al., 2017a; Veerawatananan et al., 2016). In contrast, maternal separations from P4 to P6 for 6 h per day advance the GABA shift by decreasing activity of NKCC1 and increasing expression of KCC2 (Galanopoulou, 2008). Decreased expression of NKCC1 versus KCC2 also occurs when mice are growing up in an enriched environment, with enhanced sensory and social stimuli (Baroncelli et al., 2017; He et al., 2010).

The instructive role of sensory experience becomes even more clear in animal models in which the connection between sensory input and the cortex is demolished during development, for example through ablation of the subplate. The subplate is formed by a population of transient cells that indirectly link thalamic (sensory) input to layer 4 neurons (Friauf et al., 1990). Ablation of the subplate right before eye opening prevents visual input to drive cortical activity. This prevents the postnatal increase in KCC2 in rodents and cats, including its (indirect) effects on neuronal maturation (Jantzie et al., 2015; Kanold and Shatz, 2006). A similar delay was found after sensory deprivation in turtles. Continuous dark rearing of turtles for four weeks from hatching onwards reduced KCC2 levels in the retina and prolonged the period when GABAergic responses were depolarizing (Sernagor et al., 2003).

Together, these studies demonstrate that the maturation of GABAergic signaling is tightly regulated by an intrinsic developmental program that employs trophic and other factors as signaling molecules. These intrinsic programs are under constant adjustment by hormones, (spontaneous) neuronal activity and sensory input. Future studies should further unravel the molecular mechanisms by which sensory input affects the postnatal GABA shift.

7. Consequences of a precocious or delayed GABA shift on network development

As explained above, hyperpolarizing GABA is crucial for gating synaptic plasticity (Capogna et al., 2020; Pouille and Scanziani, 2001; Wehr and Zador, 2003). The timing of the shift to hyperpolarizing GABA is therefore crucial in determining the capacity of the network to undergo developmental changes in response to (sensory) input. To gain insight into the importance of precise timing of the GABA shift, many studies have advanced or delayed the GABA shift and studied the effects on network development and behavior. The shift has been advanced experimentally by increasing the expression of KCC2 or by decreasing the expression or function of NKCC1 using genetic or pharmacological approaches. A delay in the shift has been achieved by decreasing KCC2 levels or its activity. When interpreting the experimental results, it is important to realize that manipulations of KCC2 not only affect the postnatal GABA shift, but will inevitably also alter the functions of KCC2 that are independent of Cl^-. In addition, when accelerating the GABA shift to an earlier timepoint, the influence of depolarizing GABA as a trophic factor will be automatically reduced. We will review the consequences of these manipulations in the next sections and we have summarized our conclusions in Table 1.

Table 1
Effects of manipulations of the GABA shift on excitatory and inhibitory synaptic transmission.

Timing GABA shift	Type manipulation	Effect on transmission	References
Advanced GABA shift			
Embryonically	KD NKCC1, Block NKCC1, OE KCC2	Excitatory transmission decreased in adult	Akerman and Cline, 2006; Awad et al., 2018; Wang and Kriegstein, 2008b, 2011
Embryonically or first week after birth	Block NKCC1	Inhibitory transmission transiently decreased ~4 weeks after manipulation	Deidda et al., 2015a; Nakanishi et al., 2007*; Wang and Kriegstein, 2008b, 2011
Embryonically or first week after birth	OE KCC2	Inhibitory transmission increased ~5–12 days after manipulation	Akerman and Cline, 2006; Chudotvorova et al., 2005*
Second week after birth	Block NKCC1, OE KCC2	Inhibitory transmission normal ~7 days after manipulation	Succol et al., 2012*
Second week after birth	Block shunting GABA	Excitatory transmission increased 5 days after manipulation	Salmon et al., 2020
Delayed GABA shift			
Third week after birth	KD KCC2	Inhibitory transmission normal ~7 days after manipulation	Succol et al., 2012*
Third week after birth	Block KCC2	Inhibitory transmission decreased ~7 days after manipulation	Succol et al., 2012*
Fourth week after birth	KCC2E/+ mice	Excitatory transmission transiently increased at P15 Inhibitory transmission transiently decreased at P15	Pisella et al, 2020

* These studies were performed in dissociated cultures. Indicated timing is equivalent *in vivo* timing (e.g. manipulations starting at DIV0 in cultures made from P7 mice are considered equivalent to the second week after birth), but developmental timing may partially reset in culture.

7.1. Advancing the postnatal GABA shift

Advancing the GABA shift prenatally has severe consequences for the development of glutamatergic synapses. Knockdown or pharmacological inhibition of NKCC1 from E15, which induces hyperpolarizing GABAergic responses already at P0, results in a reduction in glutamatergic synapses 2–4 weeks after birth, which lasts until adulthood. Timing is crucial, as miniature EPSC frequency is not affected when NKCC1 is blocked only embryonically (E15−19) or only postnatally (P0-7) (Wang and Kriegstein, 2011, 2008b). The effect of depolarizing GABA on glutamatergic synapse formation depends on its ability to activate NMDA receptors (Wang and Kriegstein, 2008b). A similar decrease in glutamatergic synapses was found after advancing the GABA shift via early overexpression of KCC2 in rodents and Xenopus (Akerman and Cline, 2006; Awad et al., 2018). Importantly, in both studies this effect was shown to depend on Cl^- transport. As explained above, the developmental shift in intracellular Cl^- does not precisely parallel the shift from excitatory to inhibitory GABA. During the transition period in which GABA is still depolarizing, but already inhibits network activity through shunting, depolarizing GABA actually constrains glutamatergic synapse formation in the hippocampus. Blocking GABA for 48 h during this period therefore results in an increase in miniature EPSCs and spine density (Salmon et al., 2020). Together, these results show that depolarizing GABA promotes the formation glutamatergic synapses via NMDA receptor activation during a short developmental window, which closes when GABA signaling becomes inhibitory. Missing this window, by shifting GABA too early, perturbs glutamatergic connectivity for life.

The role of depolarizing GABA in inhibitory synapse formation seems more complex. A precocious GABA shift by decreasing NKCC1 activity reduces the number of inhibitory synapses only transiently (Deidda et al., 2015a; Nakanishi et al., 2007; Wang and Kriegstein, 2011). This transient decrease occurs three to four weeks after the onset of the NKCC1 manipulation and may reflect an indirect effect of glutamatergic alterations (Wang and Kriegstein, 2008b). However, when a precocious GABA shift is induced via early overexpression of KCC2, the opposite occurs: GABAergic transmission actually increases (Akerman and Cline, 2006; Chudotvorova et al., 2005). Importantly, these effects are mediated by changes in intracellular Cl^- (Akerman and Cline, 2006). In contrast to the transient and delayed decrease in GABAergic transmission seen after removal of NKCC1, overexpression of KCC2 results in an immediate increase in GABAergic transmission. It is possible that low levels of KCC2 limit the development of inhibitory synapses during early postnatal development. A mechanism remains elusive, but it would be interesting to further explore interactions between KCC2, $GABA_A$ receptor subunit α1 (Huang et al., 2012) and NL2 (Blundell et al., 2009).

7.2. Delaying the postnatal GABA shift

It is technically more challenging to delay the GABA shift. Complete KO of KCC2 in mice is lethal after birth as a result of respiratory failure (Hübner et al., 2001). Therefore, complete absence of KCC2 can only be investigated in embryonic tissue. Synaptic changes have been reported in KCC2 KO embryos, even though embryonic KCC2 levels do not affect GABAergic reversal potentials at this age (Khalilov et al., 2011; Li et al., 2007). Several alternative mouse models have been developed in which KCC2 expression is not absent, but strongly reduced (5–20 % remaining expression) (Anacker et al., 2019; Tornberg et al., 2005; Woo et al., 2002). Alterations in glutamatergic and GABAergic transmission have been described in these models, but it remains unclear if these are due to a loss of KCC2s structural role or insufficient GABAergic hyperpolarization (Anacker et al., 2019; Riekki et al., 2008). To study the consequences of a delayed GABA shift while preserving the Cl^--independent function of KCC2, mouse models were developed recently in which KCC2 activity is decreased by interfering with post-translational

modifications of KCC2. In KCC2 S940A mice KCC2 levels are normal, but KCC2 phosphorylation at serine (S) residue 940 is prevented, resulting in a postnatal delay of the GABA shift by approximately one week (Moore et al., 2019). In $KCC2^{E/+}$ mice, phosphomimic mutations of KCC2 at threonine (T) residues 906 and 1007 result in a delay of the postnatal GABA shift by ~ two weeks in the hippocampus (Pisella et al., 2019). At P15, excitatory transmission is increased in $KCC2^{E/+}$ slices, whereas inhibitory transmission is decreased compared to controls, but excitatory and inhibitory transmission were comparable to controls again at P30 after the GABA shift was complete (Pisella et al., 2019).

7.3. Behavioral consequences

The measured effects on synaptic currents after an early or late postnatal GABA shift are relatively subtle and sometimes only transient. However, these synaptic changes occur at a developmental period in which crucial decisions are made for adult connectivity and function (Takesian and Hensch, 2013). A postnatal GABA shift which is not coordinated with cortical activity patterns and sensory input may cause permanent alterations in brain connectivity and therefore function. Subtle changes in synaptic driving force or activity can gate developmental plasticity and may therefore have long-lasting consequences for neuronal circuits. Indeed, several studies have demonstrated that small changes to the timing of the postnatal GABA shift, in either direction, are associated with alterations in behavior that last until adulthood. For instance, mice with an accelerated GABA shift through inhibition of NKCC1 or enhanced KCC2 function show a developmental delay in motor coordination and strength, decrease in anxiety, enhanced auditory reactivity, increased social behavior, a slight acceleration in the rate of learning and improved long-term memory function in adulthood (Moore et al., 2019; Wang and Kriegstein, 2011). A transient reduction in inhibitory transmission after bumetanide treatment from P3-8 was shown to prolong the critical period for visual plasticity (Deidda et al., 2015a). On the other hand, mice with reduced KCC2 levels display reduced social behavior and impaired sensory sensitivity and long term memory, along with increased anxiety-like behavior and seizure susceptibility and decreased social interaction (Anacker et al., 2019; Delpire and Mount, 2002; Moore et al., 2019; Pisella et al., 2019; Tornberg et al., 2005). These studies clearly underscore the importance of proper timing of the GABA shift for behavior later on. A recent study showed that behavioral defects in adulthood are also evoked by a transient elevation in neuronal activity, induced with kainic acid after birth (P6 to P15) (Friedman and Kahen, 2019). Together, these results show that the timing of the postnatal GABA shift needs to be coordinated with cortical activity patterns and sensory input to assure proper network development and life-long function.

8. Implications for translational research

Expression studies on postmortem brains indicate that a developmental increase in the function of KCC2 versus NKCC1 takes place in humans in the first year after birth (Kharod et al., 2019). In patients with autism spectrum disorder (ASD) and other neurodevelopmental disorders (NDDs) altered expression levels of Cl^- transporters have been found. ASD is associated with an elevated risk for epilepsy and other electroencephalography abnormalities (Buckley and Holmes, 2016), along with perturbations in the regulatory domain of KCC2 (Merner et al., 2015). Down syndrome is associated with increased NKCC1 levels (Deidda et al., 2015b), Rett syndrome with reduced KCC2 levels (Duarte et al., 2013) and Tuberous Sclerosis Complex and Dravet syndrome with both increased NKCC1 and reduced KCC2 levels (Ruffolo et al., 2018, 2016; Talos et al., 2012). These findings suggest that the GABA shift is delayed or perhaps even entirely absent in patients with various NDDs. In addition, excessive leptin, inadequate thyroid hormone and oxytocin signaling, which may also delay the GABA shift, have been implicated in the development of ASD (Ashwood et al., 2008; Modi and Young, 2012; Román et al., 2013).

A delay in the GABA shift due to an elevated ratio of NKCC1 to KCC2 activity has also been observed in several monogenetic animal models of NDDs, including mouse models for Fragile X syndrome (FMR1 KO mice) (He et al., 2014; Smalley et al., 2020a; Tyzio et al., 2014) and DiGeorge syndrome ($Lgdel^{+/-}$ mice) (Amin et al., 2017), as well in environmental ASD rodent models, through in utero exposure to immunogenic stimuli (Corradini et al., 2017; Fernandez et al., 2018) or valproate (Roux et al., 2018; Tyzio et al., 2014). The postnatal GABA shift seems even completely absent in rodent models for Rett (Mecp2 KO mice) and Down syndrome (Ts65Dn mice), in which depolarizing GABAergic actions and an elevated ratio of NKCC1 versus KCC2 were found in adulthood (Banerjee et al., 2016; Deidda et al., 2015b; Duarte et al., 2013; Lozovaya et al., 2019; Tang et al., 2016).

In an increasing number of studies, administration of the NKCC1 inhibitor bumetanide around birth is used to restore postnatal GABAergic driving force and to correct early alterations in network activity (Amin et al., 2017; Fernandez et al., 2018; Pisella et al., 2019). In many cases, inhibition of NKCC1 results in a (partial) rescue of many behavioral defects in mice (He et al., 2019; Lozovaya et al., 2019; Savardi et al., 2020; Tyzio et al., 2014). The first studies in human patients also indicate that administration of NKCC1 inhibitor bumetanide to young ASD patients can attenuate the severity of their symptoms, with no major side effects on cognitive performance in multiple clinical trials (Hadjikhani et al., 2018; Lemonnier et al., 2017, 2012; Lemonnier and Ben-Ari, 2010; van Andel et al., 2020; Zhang et al., 2020) (recently reviewed by (Kharod et al., 2019)). This underscores the crucial impact of precise timing of the postnatal GABA shift on brain function and behavior later in life. It remains unclear how the precise therapeutic window and expected effects depend on the underlying cause for the delayed shift.

These results corroborate that sustained GABAergic depolarization affects early postnatal activity levels, with long-lasting consequences for behavior. An incomplete or delayed GABA shift may contribute to behavioral symptoms in (a subset of) NDD patients. Rectifying postnatal activity by decreasing intracellular Cl^- levels may constitute a promising therapy for these patients. Another interesting, but mostly unexplored, possibility would be to rescue the GABA shift through sensory enrichment (He et al., 2010; Weitlauf et al., 2017).

9. Conclusions and final remarks

In the mature brain, hyperpolarizing GABAergic inhibition is essential for regulating information processing by counterbalancing glutamatergic excitatory transmission. Glutamatergic synapses emerge around birth in the rodent brain, but crucial neurodevelopmental events take place already when glutamatergic transmission is still scarce and most neuronal activity is locally and spontaneously generated, independent of external sensory input. At this early stage depolarizing GABAergic currents instruct the entire developmental sequence of local network establishment. The function of depolarizing GABA changes during each step, from facilitating the proliferation of stem cells, mediating the migration of precursors, outgrowth of neurites and maturation of synapses and sustaining early activity patterns in the hippocampus.

Once the rough layout is present and postnatal activity becomes sensory driven (Lohmann and Kessels, 2014; Toyoizumi et al., 2013) KCC2 activity increases and GABA shifts from being depolarizing to hyperpolarizing. This postnatal GABA shift represents the last shift in a series of developmental GABA shifts. Hyperpolarizing GABA is required to carefully select the optimal neural representations from many competing inputs that increasingly bombard the developing brain. When the postnatal GABA shift and increase in thalamocortical inputs are not mutually coordinated, network function remains altered for life.

Although some (external and internal) factors have been identified that guide the developmental GABA shifts, the precise molecular

mechanisms remain to be elucidated, in particular for the postnatal shift to hyperpolarizing GABA. It also remains unclear when GABAergic hyperpolarization is exactly required and why the timing of the postnatal GABA shift is altered in ASD and related NDDs. It is unknown if altered levels of the Cl^- cotransporters are a direct effect of genetic or environmental factors, or that the shift is delayed because earlier developmental 'checkpoints' are missed. Subtle changes in the perinatal network may cause failure to activate signaling programs that normally promote the rise in KCC2 expression and shift to hyperpolarizing GABA. It will be particularly interesting to further examine the link between sensory input and the timing of the postnatal GABA shift, particularly in the context of NDDs. Improving our understanding of GABAergic signaling in brain development may open up new strategies to alleviate behavioral impairments in ASD and related NDDs in the future.

Author contributions

CP and CJW conceived and wrote the paper together.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

This research was supported by a TOP grant 9126021 from ZonMw. The authors thank Christian Lohmann, Martien Kas and Lotte Herstel for critically reading the manuscript.

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