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$GABA_A$, NMDA and AMPA receptors: a developmentally regulated 'ménage à trois'

Yehezkel Ben-Ari, Roustem Khazipov, Xavier Leinekugel, Olivier Caillard and Jean-Luc Gaiarsa

The main ionotropic receptors ($GABA_A$, NMDA and AMPA) display a sequential participation in neuronal excitation in the neonatal hippocampus. GABA, the principal inhibitory transmitter in the adult CNS, acts as an excitatory transmitter in early postnatal stage. Glutamatergic synaptic transmission is first purely NMDA-receptor based and lacks functional AMPA receptors. Therefore, initially glutamatergic synapses are 'silent' at resting membrane potential, NMDA channels being blocked by Mg^{2+}. However, when GABA and glutamatergic synapses are coactivated during the physiological patterns of activity, $GABA_A$ receptors can facilitate the activation of NMDA receptors, playing the role conferred to AMPA receptors later on in development. Determining the mechanisms underlying the development of this 'ménage à trois' will shed light not only on the wide range of trophic roles of glutamate and GABA in the developing brain, but also on the significance of the transition from neonatal to adult forms of plasticity.

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THE DEVELOPMENT AND FORMATION of neuronal circuits is a relatively rapid sequence of events during which neurones migrate, arborize and establish synaptic connections, some of which are stabilized and others eliminated. Neuronal activity appears to play a crucial role in coordinating this formation: 'neurones that fire together wire together'[1–3]. As in adult forms of synaptic plasticity, this modulation is mediated largely by increases in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) that activate a wide range of intracellular cascades. Studies on the ontogeny of membrane properties of excitable cells have revealed a

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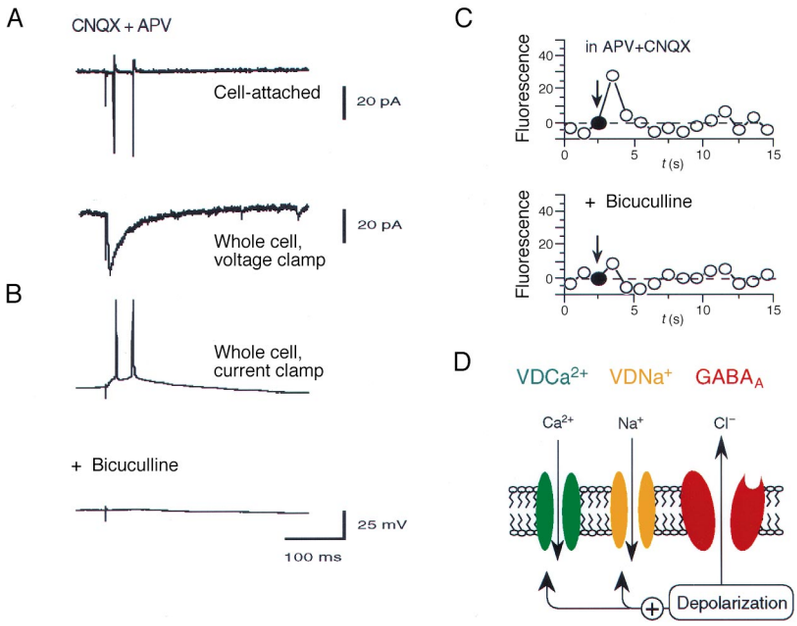

Fig. 1. ***Synaptic activation of $GABA_A$ receptors triggers action potentials and increases $[Ca^{2+}]_i$ in the neonatal rat hippocampal neurones.*** *In cell-attached recordings of postnatal day 2 (P2) CA3 stratum radiatum interneurone, action potentials were elicited by electrical stimulation in the presence of ionotropic glutamate-receptor antagonists CNQX (10 μM) and APV (50 μM)* **(A, upper trace)**. *Immediately after entry to whole-cell, the same electrical stimulation elicited $GABA_A$ PSCs in voltage-clamp mode* **(A, lower trace)** *and $GABA_A$ PSPs in current-clamp mode* **(B, upper trace)**. *Synaptic response and action potentials were blocked by 10 μM bicuculline* **(B, lower trace)**. **(C)** *Electrical stimulation also elicited an increase of $[Ca^{2+}]_i$ fluorescence in CA3 pyramidal neurone (P5) loaded extracellularly by the Ca^{2+}-sensitive dye fluo3-AM.* Reproduced, with permission, from Ref. 28. **(D)** *Scheme of the interactions between $GABA_A$ receptors and voltage-gated Na^{2+} and Ca^{2+} channels in immature neurones.*

dramatic pattern of changes in voltage- and receptor-operated channels and ionic gradients that may result in different roles of the major neurotransmitters at sequential developmental steps[4].

In the present review, we focus on the recent progress made in understanding the functional maturation of GABAergic and glutamatergic synaptic transmissions in the CNS. Recent studies have revealed unique interactions between GABA, glutamate and voltage-gated ionic channels in rat neonatal hippocampal neurones. As a consequence, a pattern of network-driven activity (so-called Giant Depolarizing Potentials, GDPs[5]) is generated, associated with synchronous $[Ca^{2+}]$ oscillations. These results provide a new framework within which to understand the activity dependent formation of neuronal circuits in the developing brain.

Developmental changes in GABAergic transmission.

Functional $GABA_A$ receptors are expressed in neurones as early as embryonic stages and investigations by different groups have led to the conclusion that a transient excitatory action of GABA, via $GABA_A$ receptors, represents a general feature of the developing neurones. Activation of $GABA_A$ receptors depolarizes neuroblasts and immature neurones in all regions of the CNS studied so far, including spinal cord[6–9], hypothalamus[10], cerebellum[11], cortex[12–14], hippocampus[1,5,15,16] and olfactory bulb[7]. This depolarization is not due to unusual properties of neonatal $GABA_A$ channels[18] but rather to an elevated intracellular Cl^- concentration probably resulting from developmental changes in $[Cl^-]_i$ homeostasis systems[7,17–21].

The depolarizing effects of GABA result in unique interactions between $GABA_A$ and voltage- and receptor-operated ionic channels. In contrast to their action on adult neurones, activation of $GABA_A$ receptors depolarizes immature neurones and this depolarization reaches the threshold for Na^+ action potential generation, meaning that GABA operates as an excitatory neurotransmitter (Fig. 1A,B). Originally observed in the hippocampal formation using intracellular recordings[5,16], the depolarizing and excitatory effects of GABA have now been demonstrated in many other immature brain structures using approaches that do not modify $[Cl^-]_i$, such as voltage-sensitive dyes[17,21], patch-clamp recordings in the cell-attached mode (Fig. 1)[7,23–25] or perforated patch clamp using the chloride-impermeable ionophore, gramicidin[8,13,26,27].

As shown using confocal microscopy with fluorescent Ca^{2+}-sensitive dyes, the depolarizing action of GABA also activates voltage-dependent Ca^{2+} channels, thereby increasing the $[Ca^{2+}]_i$) (Refs 9–11,13,23, 26–30). Increases of $[Ca^{2+}]_i$ produced by application of GABA or $GABA_A$ receptor agonists[10,30,31] are prevented by bicuculline, by Ca^{2+}-channel blockers and by clamping the cells at hyperpolarized potentials. These effects have been observed in immature neurones in culture[9–11,23,26,27] and in acute brain slices[13,28,30]. Importantly, synaptically released GABA also increased $[Ca^{2+}]_i$ in immature hippocampal neurones[28] (Fig. 1C).

Thus, GABA operates as an excitatory transmitter in neonatal neurones. A number of issues concerning the role of GABA in the developing brain remain to be addressed. One of them is whether and how GABA is released and activates its targets at the stages prior to synaptogenesis when postsynaptic $GABA_A$ receptors are expressed and GABA exerts well-documented trophic actions[13,31,32]. Second, several recent studies have indicated that GABA might have dual effects on immature neurones: in addition to its excitatory action due to depolarization, GABA can also exert inhibitory shunting effects via increase of the membrane conductance[26], as it does in adult neurones[33]. To what extent this shunting mechanism affects the interactions between receptor- and voltage-gated channels and the network activity remains to be studied. It will also be important to determine the factors responsible for the shift from excitatory to inhibitory action of GABA as well as the developmental gradients of somatic and dendritic GABAergic innervations, that subserve different functions in adult neurones[34,35]. Another issue concerns the delayed development of $GABA_B$ receptor-mediated postsynaptic inhibition. Postsynaptic $GABA_B$ receptor-mediated responses, that is, the activation of K^+ and inhibition of Ca^{2+} currents, are absent from embryonic and neonatal rat hippocampal and neocortical neurones until the end of the first postnatal week of life[12,36,37]. The reasons for this delayed maturation of postsynaptic $GABA_B$ receptor-mediated inhibition are not yet well understood; it seems to be due to a lack of coupling between receptors, G proteins and K^+ or Ca^{2+} channels[36], rather than to a late development of receptors[37,38]. In striking contrast, the presynaptic inhibition mediated by $GABA_B$ receptors is already functional at birth[36,37] and provides powerful inhibitory control of the neonatal network activity[39].

The importance of GABAergic excitation for the interactions between neurones in the immature network is reinforced by the fact that establishment of GABAergic synaptic connections precedes the appearance of glutamatergic synapses[1,5,40,41] that in addition initially lack functional AMPA receptors, and thus are silent at resting membrane potential[41–44]. Therefore, prior to glutamatergic innervation and at the time when AMPA receptors are relatively quiescent, GABAergic innervation provides an important source for the neuronal excitation.

Sequential development of NMDA and AMPA receptor-mediated glutamatergic synaptic transmission

Recent studies have also revealed that glutamatergic synaptic transmission undergoes significant changes during development. The probably major observation that has been made recently in this field is that glutamatergic transmission is initially purely NMDA receptor-mediated, without any significant contribution of AMPA receptors[41–44]. Since the voltage-dependent Mg^{2+} block of NMDA channels is as efficient in neonatal hippocampal neurones as it is in adults[45,46], these premature synapses are 'silent' at resting membrane potential. In CA1 pyramidal neurones, starting from postnatal day 2 (P2), the first glutamatergic synapses that are established, are 'silent'; the percentage of 'silent' synapses progressively decreases between P2 and P5 (Fig. 2)[41,43]. Similar observations have been made for developing thalamocortical connections[44] and in the frog optic tectum[42]. It has been suggested that glutamatergic 'silent' synapses could result from the absence of functional AMPA receptors on the postsynaptic site. Another hypothesis is that 'silent' synapses might be attributed to the spillover of glutamate from a presynaptic bouton onto the postsynaptic site of an adjacent cell[47]. Since NMDA receptors have a much higher affinity for glutamate (by about 500 times) than AMPA receptors[48], they would be preferentially activated by glutamate spillover. A related hypothesis that has not been explored yet is that 'silent' synapses might be due to spillover of glutamate from growth cones to adjacent dendrites. Whatever the mechanism, existence of 'silent' synapses could explain the preferential contribution of NMDA receptors to synaptic transmission and network activity in the neonatal brain[4,5,30,49–55]. Additional factors that potentially contribute to the enhanced participation of NMDA receptors to synaptic transmission include the following. (1) An increased density of NMDA receptors[56]. (2) The slow decay of NMDA receptor mediated currents in neonatal cells[46,57,58], presumably due to a different subunit composition of the NMDA receptor–channel complex[59]. (3) The depolarizing action of GABA that facilitates, instead of inhibiting, the activation of NMDA receptors.

Interestingly, the conversion of 'silent' synapses into functional ones requires the activation of NMDA receptors and a Hebbian stimulation, in analogy to LTP paradigms[41–44]. However, Liao and Malinow reported that in neonatal hippocampal slices, synaptic activation of AMPA receptors can not provide the depolarization sufficient to remove the Mg^{2+} block and activate NMDA channels[43]. Recent studies demonstrated that this depolarization can be provided by GABA. Importantly, the potentiation of NMDA receptor-mediated signals by depolarizing effect of GABA has been found to occur during the physiological pattern of activity of the neonatal hippocampus, so-called GDPs[5,24,25].

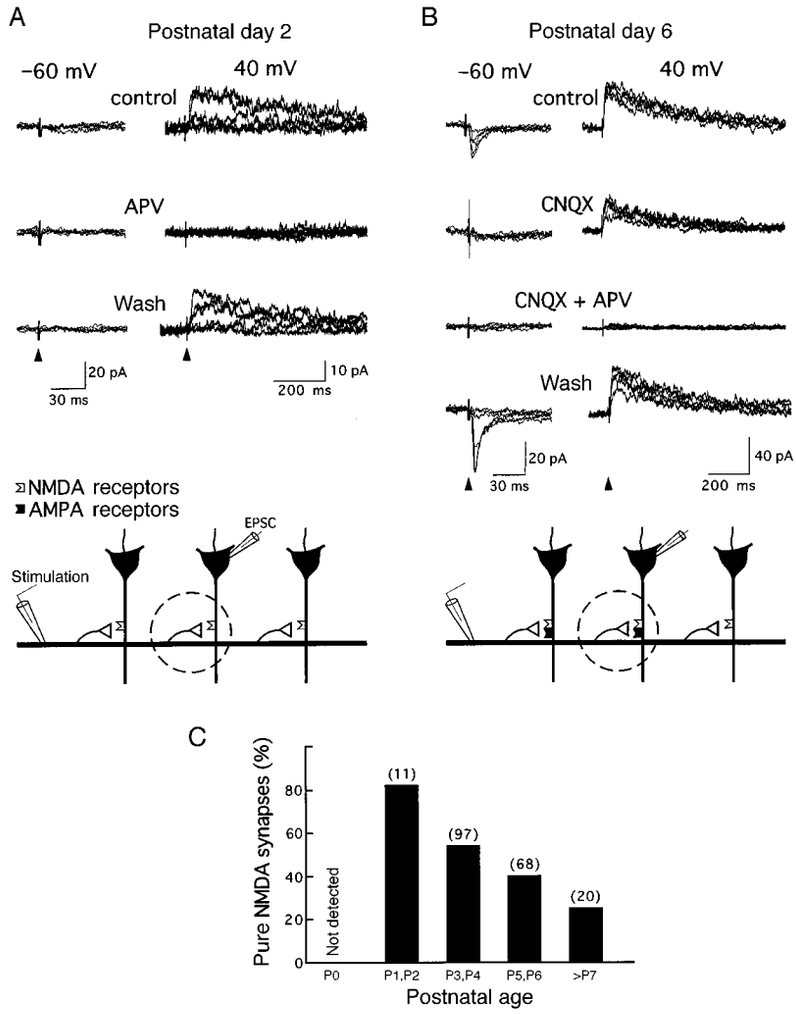

Fig. 2. ***High incidence of pure NMDA-receptor-mediated synaptic transmission in newborn rats.*** **(A)** *Whole-cell voltage-clamp recording from a CA1 pyramidal (P2). Afferent single-shock stimulation elicited EPSCs detected at a holding potential of +40 mV, but not at –60 mV (control). These EPSCs were completely and reversibly blocked by APV (50 μM). Bottom, the experimental result illustrated schematically.* **(B)** *EPSCs recorded in a hippocampal CA1 pyramidal neurone from a 6-day-old rat. In addition to the NMDA receptor component, these EPSCs also reveal an AMPA component at –60 mV (control) that is reversibly blocked by CNQX (5 μM). Bottom, a model of the corresponding synapse with colocalized AMPA and NMDA receptors. Recordings in* (A) *and* (B) *display superposition of 5 consecutive synaptic responses. Arrowheads indicate the time of stimulation.* **(C)** *The proportion of pure NMDA synapses decreases during the first week of postnatal development. Bars represent the percentage of synapses producing only NMDA receptor-mediated EPSCs over the total number of synapses (NMDA-mediated plus conducting synapses). The numbers in parentheses above the bars indicate the total number of synaptic inputs tested per age. At P0, 400 stimulation sites in eight cells were recorded. Even with the minimal stimulation used here, there is no certainty of stimulating a single input axon.* Reproduced, with permission, from Ref. 41.

Synergistic excitatory actions of $GABA_A$ and NMDA receptors

In adult neurones, GABAergic inhibition prevents the activation of NMDA receptors thus inhibiting the induction of NMDA receptor-dependent forms of synaptic plasticity (Refs 60–62, but see also Ref. 22). A different situation prevails in the neonatal brain, in which GABA provides depolarization instead of hyperpolarization. Indeed, $GABA_A$ receptor-mediated depolarization attenuates the voltage-dependent Mg^{2+}

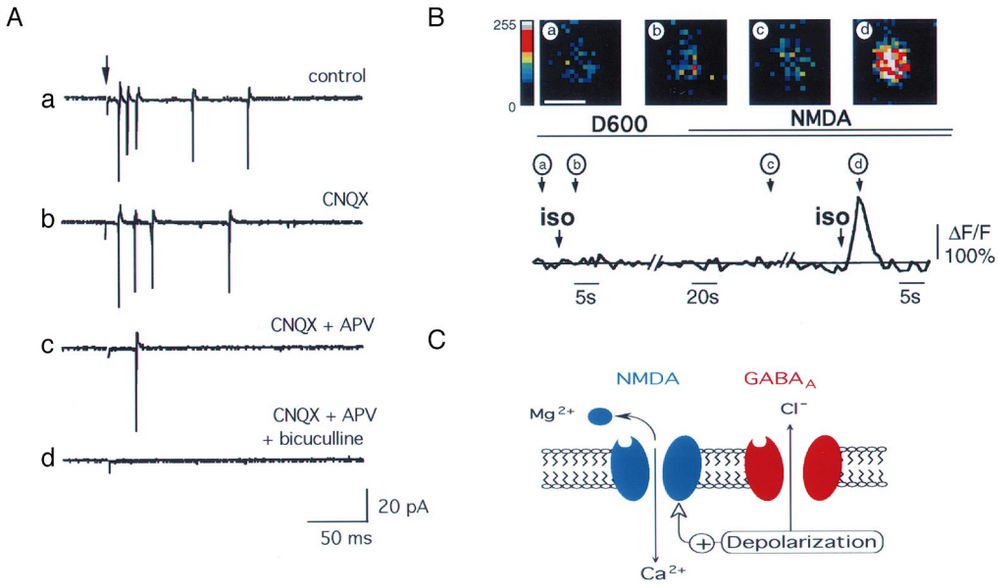

Fig. 3. ***GABA potentiates the activity of NMDA receptors in the neonatal hippocampus.*** **(A)** *Synaptically elicited responses in neonatal CA3 pyramidal neurons (P5) recorded in cell-attached configuration.* **(a)** *In control conditions, electrical stimulation elicited a burst of five action potentials.* **(b)** *The number of action potentials was slightly affected by AMPA-receptor antagonist CNQX (10 μM), and* **(c)** *strongly reduced by further addition of NMDA-receptor antagonist APV (50 μM).* **(d)** *The remaining response was blocked by $GABA_A$ receptor antagonist bicuculline (10 μM).* **(B)** *A CA3 pyramidal neuron (P5) was loaded extracellularly with the Ca^{2+}-sensitive dye fluo3-AM, and the slice continuously superfused with the voltage-gated Ca^{2+}-channel blocker, D600 (50 μM). Focal pressure ejection of a $GABA_A$-receptor agonist, isoguvacine (100 μM), or bath application NMDA (10 μM) had no effect on $[Ca^{2+}]_i$ fluorescence. However, a combined activation of $GABA_A$ and NMDA receptors resulted in significant increase of $[Ca^{2+}]_i$ fluorescence.* **(C)** *Scheme of the interactions between $GABA_A$ and NMDA receptors in immature neurones.* Reproduced, with permission, from Ref. 25.

block of single NMDA channels recorded in cell-attached configuration from neonatal CA3 hippocampal neurones (Fig. 3A). This effect results also in an increased Ca^{2+} influx via NMDA channels, recorded using confocal microscopy with the permeant dye Fluo-3 AM (Fig. 3B). Moreover, potentiation of NMDA channels by depolarizing GABA action occurs also during synaptic responses. In cell-attached recordings from P2–5 CA3 pyramidal cells and GABAergic interneurones, the burst of four or five action potentials elicited by electrical stimulation was slightly reduced by the AMPA receptor antagonist CNQX[24,25] (Fig. 3Aa–b). In the presence of CNQX, blockade of $GABA_A$ receptors by bicuculline completely blocked the response and only one or two bicuculline-sensitive action potentials could be elicited after blockade of NMDA receptors by APV (Fig. 3Ac–d). This situation is in contrast with the synaptic responses a week later: as found in adults, the responses are composed of a single action potential and are completely blocked by CNQX. We suggest that the main receptor-operated channels (that is, $GABA_A$, NMDA and AMPA receptors, respectively) display an activity dependent sequential participation to neuronal excitation.

If $GABA_A$ receptors play an important role in the activation of NMDA receptors, one can expect that NMDA receptor-dependent forms of synaptic plasticity will be enhanced by $GABA_A$ receptors in neonates, in contrast to the situation in adults[60–62]. Indeed, in neonatal hippocampal CA3 pyramidal neurons, a LTD of $GABA_A$ receptor-mediated synaptic potentials can be induced by a tetanus that provides synchronous activation of $GABA_A$ and NMDA receptors[63]. This LTD is prevented by antagonists of either $GABA_A$ or NMDA receptors, suggesting that the synergistic excitatory actions of $GABA_A$ and NMDA receptors are required for the induction of this form of plasticity[63] (see Box 1). Therefore the Hebbian 'coincidence detector' role of NMDA receptors is not restricted to the modulation of the classical AMPA receptor-mediated excitatory transmission: early in development, NMDA receptors may control the efficacy of GABAergic transmission, the principal mediator of excitation at this stage. This further reinforces the view that GABA receptors in the developing hippocampus *de facto* play the role conferred on AMPA receptors in adult. It remains to be elucidated whether other NMDA receptor-dependent forms of synaptic plasticity, such as LTP–LTD of AMPA receptor-mediated component of EPSPs, require synergistic excitatory actions of $GABA_A$ and NMDA receptors. A particularly intriguing question in this field is whether induction of LTP and expression of functional AMPA receptors in initially 'silent' synapses also requires synergistic interactions between $GABA_A$ and NMDA receptors.

GDPs and associated $[Ca^{2+}]_i$ oscillations

Synchronized neuronal activity and $[Ca^{2+}]_i$ oscillations have been reported in a wide range of central and peripheral systems[5,64–69] and appear to be a fundamental feature of developing brain structures. Although the mechanisms, including gap junctions[64,65,70,71] or synaptic transmission[5,66,69,72], involved in their generation may differ, oscillations are thought to play a central role in the development and formation of functional neuronal circuits. In embryonic spinal cord, $[Ca^{2+}]_i$ oscillations shape neuronal differentiation and morphogenesis[64], Ca^{2+} spikes being required for the expression of $GABA_A$ receptors and K^+ channels, whereas neuritic extension appears to be modulated by Ca^{2+} waves. In the visual system, waves propagate from retina to the lateral geniculate nucleus[67] and desynchronized patterns of discharges between the inputs of both eyes during a critical period of development are essential for the expression of ocular dominance[3]. In the neocortex, synchronized Ca^{2+} oscillations within restricted groups of neurones might underlie the formation of functional columns and barrels[65].

The hippocampus during the first week of postnatal life is also characterized by periodical synchronous network driven GDPs[5,71,73,74]. GDPs are observed in CA3–CA1 pyramidal cells until the end of the first postnatal week and they are replaced during the second week by Large Hyperpolarizing Potentials[5]. Initially, GDPs were described as $GABA_A$ receptor-mediated events as they were blocked by bicuculline and had a reversal potential close to E_{Cl^-} (Refs 5,71,73,74). Therefore, GDPs were suggested to result from the synchronous discharges of the interneuronal network.

Box 1. LTD and LTP of neonatal GABAergic synapses

Long term potentiation (LTP) and depression (LTD) are the two classical forms of activity-dependent synaptic plasticity at excitatory glutamatergic synapses. Electrical stimulation or other experimental paradigms that remove the voltage-dependent Mg^{2+} block from NMDA channels and increase $[Ca^{2+}]_i$ generate long-term changes in synaptic efficacy that are expressed by AMPA receptors[a]. It appeared recently that not only glutamatergic synapses but also GABAergic synapses are subject to short-term[b–d] and long-term[e–l] changes in which activation of pre- or postsynaptic neurones, or both, and subsequent rise in $[Ca^{2+}]_i$ are required.

Both NMDA-dependent LTD and NMDA-independent LTP of $GABA_A$ receptor-mediated synaptic transmission ($LTD_{GABA\text{-}A}$ and $LTP_{GABA\text{-}A}$) have been reported in the young visual cortex[i–k] and neonatal hippocampus[l] following a high frequency train. An increase in $[Ca^{2+}]_i$ is a common trigger for the induction of GABAergic synaptic plasticity but the source of Ca^{2+} and the mechanisms leading to this increase differ in the visual cortex and hippocampus. In the visual cortex, the induction of $LTP_{GABA\text{-}A}$ requires the activation of postsynaptic G protein-coupled receptors leading to $InsP_3$-induced Ca^{2+} release, but does not require the activation of $GABA_A$ receptors[k]. NMDA-dependent $LTD_{GABA\text{-}A}$ is induced only when hyperpolarizing $GABA_A$ receptor-mediated potentials are blocked during the tetanic stimulation to allow activation of NMDA channels[i]. Therefore, in the visual cortex, activation of $GABA_A$ receptors does not participate in the induction of plasticity at GABAergic synapses; in fact it prevents the induction of $LTD_{GABA\text{-}A}$. A completely different situation prevails in the neonatal hippocampus: activation of $GABA_A$ receptors is required for the induction of $LTD_{GABA\text{-}A}$ and $LTP_{GABA\text{-}A}$. Indeed, $GABA_A$ receptors provide the depolarization that releases Mg^{2+} block of NMDA channels to induce LTD[l] or activates voltage-gated calcium channels to induce LTP[l]. Thus, in the neonatal hippocampus, LTD and LTP of GABAergic synaptic transmission are unique in that the induction and expression are mediated by $GABA_A$ receptors, in analogy with the adult forms of LTD and LTP that are induced and expressed by AMPA receptors in glutamatergic synapses.

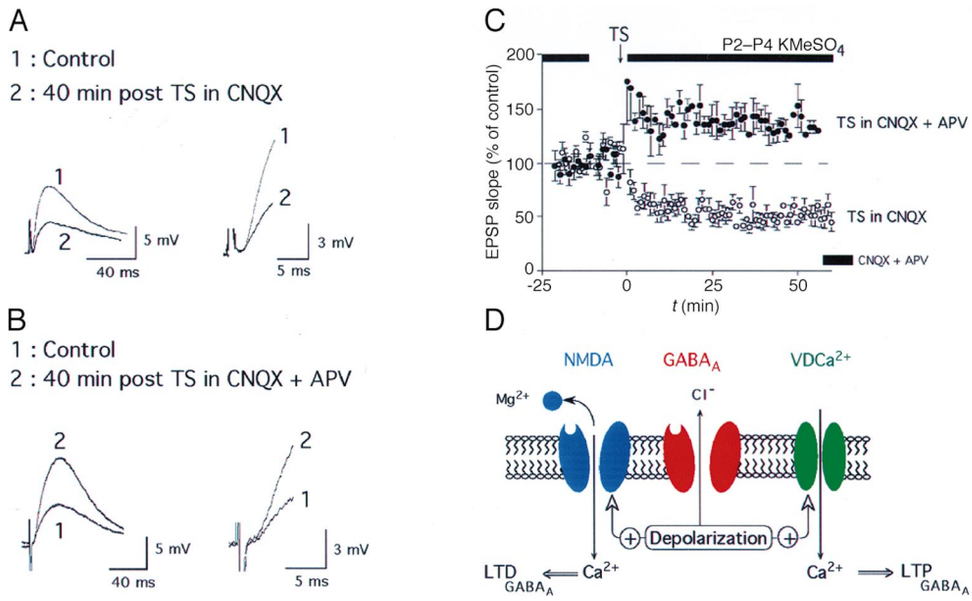

Fig. ***Activity-dependent synaptic plasticity of GABAergic transmission in neonatal rat hippocampus.*** *Monosynaptic $GABA_A$ receptor-mediated PSPs evoked by electrical stimulation in presence of ionotropic glutamate receptor antagonists CNQX (10 μM) and APV (50 μM) in P2 CA3 pyramidal neurone* **(A and B, traces 1)**. *Tetanic stimulation in the presence of CNQX alone induced LTD of $GABA_A$ PSPs* **(A, traces 2)** *whereas tetanic stimulation in the presence of CNQX and APV induced LTP of $GABA_A$ PSPs* **(B, traces 2)**. **(C)** *Graph illustrating the time course of LTD and LTP of $GABA_A$ PSPs.* **(D)** *Scheme of the mechanisms underlying LTD and LTP of GABAergic synaptic transmission.* Reproduced, with permission, from Ref. l.

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Recent studies using patch-clamp recordings and confocal microscopy from CA3 pyramidal cells and interneurones[24,25] showed that GDPs result from the synchronous discharge of pyramidal cells and GABAergic interneurons (Figs 4A,B) and that synchronization of neuronal network discharge results from the cooperation between GABAergic and glutamatergic synaptic connections. It bears stressing that GDPs are observed in isolated CA3 islands of hippocampal slices[24], suggesting that they can be generated by a local circuit of pyramidal cells and interneurones. Cherubini and collaborators[71] have, however, suggested that hilar interneurones might play a central role in GDP induction by gap-junction coupling and intrinsic oscillations of membrane potential. Interestingly, these oscillations were paced by a hyperpolarization-activated current with properties of I_h.

In spite of the large body of evidence for trophic actions of GABA[75–78] and glutamate[3,4] in developing neurones, much less is known about how these trophic effects are exerted during physiological patterns of activity. Recent studies in the developing hippocampus[25,78,79] have provided interesting insights in this domain. Experiments using confocal microscopy and Ca^{2+} imaging have revealed that GDPs, driven by the synergistic excitatory actions of GABA and glutamate, are associated with synchronous Ca^{2+} oscillations mediated by voltage-dependent Ca^{2+} channels[25] and NMDA receptors[79] (Fig. 4C). This suggests that GDPs could be implicated in different steps of neuronal maturation. Importantly, since they provide synchronous activity of presynaptic afferents and postsynaptic $[Ca^{2+}]_i$ increases, they are likely candidates to mediate both Hebbian activity-dependent plasticity of

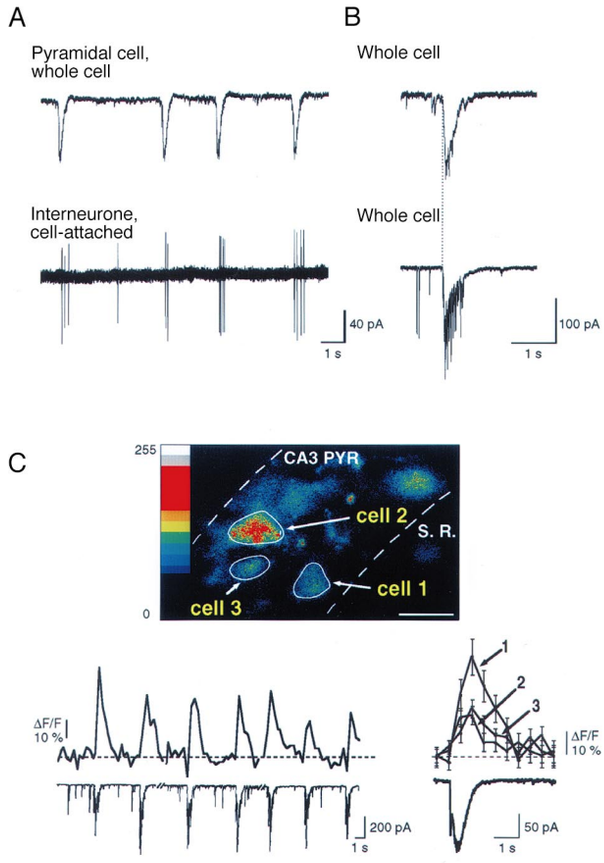

Fig. 4. ***Giant Depolarizing Potentials are associated with synchronous [Ca^{2+}]$_i$ oscillations in CA3 pyramidal neurons of neonatal hippocampal slices.*** **(A)** *Simultaneous recording of CA3 pyramidal neurone in whole-cell voltage-clamp configuration* **(upper trace)** *and stratum radiatum interneurone in cell-attached configuration* **(lower trace)**. *Bursts of action potentials in the interneurone are synchronous with GDPs in the pyramidal cell.* **(B)** *Dual whole-cell voltage-clamp recordings of CA3 pyramidal neurone and stratum radiatum interneurone, showing that GDPs are synchronously generated in both cells.* Reproduced, with permission, from Ref. 24. **(C)** *Synchronous [Ca^{2+}]$_i$ oscillations in a group of CA3 pyramidal cells loaded with fluo3-AM in a neonatal hippocampal slice* **(upper panel)**. *Synchronous increases of [Ca^{2+}]$_i$* **(middle trace)** *are associated with GDPs in the pyramidal neurone simultaneously recorded close to this group* **(lower trace)**. Reproduced, with permission, from Ref. 25.

developing synapses and formation of the hippocampal neuronal network.

Concluding remarks

The observations summarized in this review show that in an early postnatal period the hippocampal circuit shifts from one in which $GABA_A$ and NMDA receptors are the key elements to one in which AMPA and NMDA receptors act in synergy to mediate the excitatory drive (Fig. 5). Following this abrupt switch, $GABA_A$ receptors exert their inhibitory role preventing sustained excitatory and potentially excitotoxic glutamatergic activity. This general pattern is of course subject to local changes according to the developmental gradients, heterogeneity of neuronal populations within hippocampal regions and neuronal activity. We propose that the GABAergic interneuronal circuits develop prior to those of the principal glutamatergic pyramidal neurones and the first functional synapses to be formed are GABAergic and excitatory. At this early stage, at a time when glutamatergic synapses are poorly developed, GABA provides the stimulus for increases of $[Ca^{2+}]_i$ that are required for the growth of pyramidal neurones and exerts a trophic action. Glutamatergic synapses develop subsequently and transmission in these synapses is initially mediated solely by NMDA receptors. It remains to determine if the synergistic actions of $GABA_A$ and NMDA receptors and the GDPs participate in the maturation of initially silent NMDA receptor-mediated synapses and promote the expression of AMPA receptor-mediated component. Of particular interest will be also to determine how GDPs relate to *in vivo* physiological patterns of activity that occur during development. The recent development of an intact hippocampal-formation preparation that can be kept *in vitro* for over 20 hours and – in which GDPs are present[80–82] – will facilitate this research. Interestingly, GDPs are reminiscent of *in vivo* pattern of activity in adult hippocampus – so-called sharp wave bursts. Similarly to GDPs, sharp wave bursts reflect synchronous discharge of pyramidal cells and interneurones and they have been implicated in changing the synaptic connectivity of the circuitry[83]. GDPs can be an early form of sharp wave bursts using the same circuitry, with the difference that recruitment is initiated by the excitatory GABA effect and not by AMPA receptors.

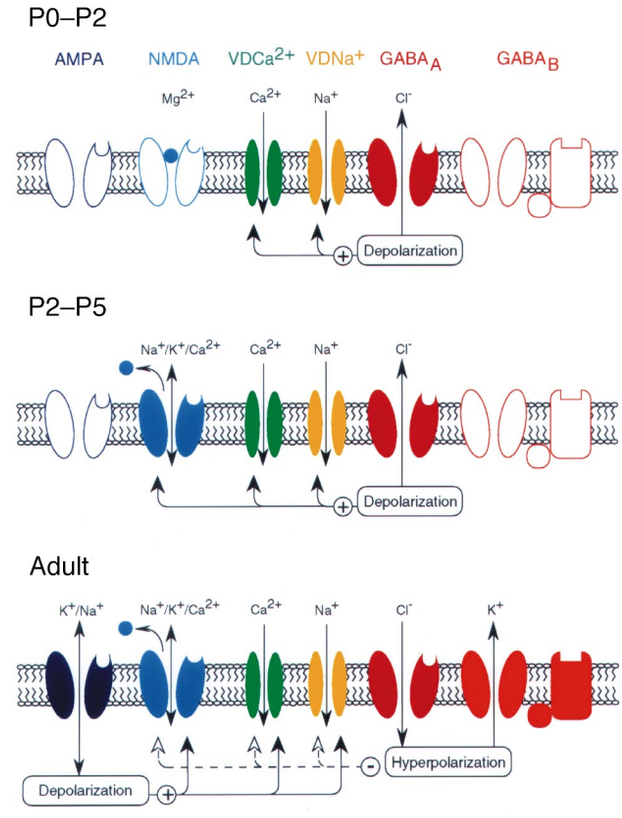

Fig. 5. ***Sequential maturation of GABAergic and glutamatergic synaptic transmission.*** *$GABA_A$ receptors, which provide membrane depolarization leading to activation of Na^+ and Ca^{2+} voltage-dependent channels, are the only source of synaptic excitation of hippocampal pyramidal cells at P0–P2. Glutamatergic synapses, which initially lack functional AMPA receptors, appear after P2 and act in synergy with GABAergic synapses, leading to the depolarizing effect of GABA releasing the voltage-dependent Mg^{2+} block of NMDA channels. At the end of the first postnatal week, the main excitatory drive is provided by the AMPA receptors whereas GABA, acting via $GABA_A$ and $GABA_B$ receptors, takes its classical inhibitory role. Open symbols, nonfunctional receptors; filled symbols, functional receptors.*

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