Long-term plasticity at GABAergic and glycinergic synapses: mechanisms and functional significance

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Activity-dependent long-term changes in synaptic efficacy are thought to be important in learning, memory formation, neuronal development and pathological states of neuronal excitability in the CNS. For the past two decades, numerous studies have investigated long-term changes in synaptic efficacy at excitatory glutamatergic synapses. Although inhibitory synapses are essential for proper functioning of the neuronal network, attention has focused only recently on describing and characterizing plasticity at these types of synapse. Not surprisingly, different forms of plasticity at GABAergic, and the closely related glycinergic, synapses have been reported in several regions of the brain. Here we review these different forms of plasticity and focus on their possible roles in developing and adult neuronal networks.

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Synaptic plasticity refers to the process by which synapses are modified in structure and function in response to different stimuli or environmental cues. Activity-dependent synaptic plasticity is thought to underlie many seemingly diverse processes, such as learning and memory, the formation of proper synaptic connections during development and the manifestation of pathological conditions.

The classical models for studying activity-dependent synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD), which represent, respectively, an increase and a decrease in synaptic strength [1]. Owing to the wide-ranging significance of long-term plasticity, considerable efforts have been made to identify the mechanisms by which synaptic changes are triggered and expressed at glutamatergic synapses [2,3]. But GABAergic interneurons also have a crucial role in shaping the activity of their target cells and cell populations [4]. Thus, the strength of inhibitory synapses will also shape the input–output relationship of neurons, the excitability of the neuronal network and the generation of network oscillations relevant to behaviour. Information on long-term plasticity at inhibitory synapses is, therefore, necessary for a full understanding of both physiological and pathological network plasticity.

In the past decade, long-term plasticity at GABAergic and glycinergic synapses has been reported in different regions of the brain. In this review, we briefly summarize the mechanisms that underlie these forms of synaptic plasticity and discuss their possible functional implications.

Long-term changes in GABAergic and glycinergic synaptic strength

GABAergic and glycinergic synapses undergo long-term plasticity

In the past decade, LTP and LTD of inhibitory synapses have been reported to occur in several regions of the brain, including the hippocampus [5–12], cortex [13–16], cerebellum [17–19], deep cerebellar nucleus [20–22], lateral superior olive [23,24] and brain stem [25,26] (Table 1). LTP of glycinergic synapses that impinge on the Mauthner cells has also been reported to occur in goldfish [27–29]. Long-term plasticity has been observed on pharmacologically isolated inhibitory postsynaptic potentials (IPSPs) and inhibitory postsynaptic currents (IPSCs) [8–10,14,23,25,26,30], and on unitary IPSCs that are evoked by directly stimulating interneurons [16,19,28,31]. These observations rule out the possibility that modifications of the excitatory inputs to interneurons underlie the long-term changes in inhibitory synaptic transmission.

Not surprisingly, several different mechanisms have been reported to contribute to the induction and maintenance of inhibitory synapses (Table 1, Box 1). A rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is important in shaping the strength of inhibitory synapses (Table 1). This increase in $[Ca^{2+}]_i$ could occur in the postsynaptic target cells (Fig. 1a–c), in the presynaptic terminals [25] or in the neighbouring astrocytes [31] (Fig. 1d). In the neonatal hippocampus [9], LTP at GABAergic synapses results from the postsynaptic opening of voltage-dependent Ca^{2+} channels (VDCCs; Fig. 1a), whereas in the cortex [15] and cerebellum [19] this process requires the release of Ca^{2+} from postsynaptic internal stores (Fig. 1c). In the neonatal [10] and adult hippocampus [7,32], LTD of GABAergic synapses is triggered by an influx of Ca^{2+} through NMDA-gated channels. Notably, the initial depolarization that leads to removal of the voltage-dependent Mg^{2+} block of NMDA channels during the conditioning protocol depends on the developmental stage (Fig. 1a,b): it is provided by $GABA_A$ receptors in neonates [10] and by AMPA receptors in adults [7].

At inhibitory synapses in the deep cerebellar nuclei, both LTP and LTD can be induced by different conditioning protocols [20,22]. A unique property of

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Table 1. GABAergic and glycinergic synapses undergo long-term change in synaptic efficacy[a]

Structure	Age	Conditioning protocol	Effect	Ca^{2+} source	Modification	Refs
Rat neocortex, pyramidal cells	P14–P16	Coincident pre- and postsynaptic firing	LTD	Postsynaptic	ND	[16]
		Delayed pre- and postsynaptic firing	LTP	Postsynaptic	ND	
Rat visual cortex, pyramidal cells	P20–P30	TS with CNQX and bicuculline	LTD	Postsynaptic NMDA receptors	ND	[13–15]
		TS with CNQX and APV	LTP	Postsynaptic Ins(1,4,5)P_3-Ca^{2+} stores	ND	
Rat hippocampus, CA3 pyramidal cells	P2–P4	TS with CNQX	LTD	Postsynaptic NMDA receptors and internal Ca^{2+} stores	↑ CV of eIPSC ↓ Sr^{2+}-induced sIPSC frequency	[8–12]
	P0–P8	TS with CNQX and APV	LTP	Postsynaptic VDCCs	↑ mIPSC frequency	
		DP with CNQX and APV	LTP	ND	Reveals latent GABAergic connections	
Guinea pig hippocampus, CA1 pyramidal cells	>P30	TS	LTD	Postsynaptic NMDA receptors	↓ $I_{GABA\text{-}A}$ amplitude	[6,7,32]
Rat hippocampus, CA1 pyramidal cells	P8–P20	Interneuron firing	LTP	$GABA_B$-induced Ca^{2+} rise in astrocytes	↓ uIPSC failure ↑ mIPSC frequency	[31]
Rat deep cerebellar nuclei	P7–P9	LFS with DNQX	LTD	Postsynaptic NMDA receptors	↓ $I_{GABA\text{-}A}$ amplitude	[21,22,33]
		DP with DNQX and APV	LTP	Postsynaptic VDCCs	↑ mIPSC frequency	
				ND	↑ $I_{GABA\text{-}A}$ amplitude	
	P11–P15	RD-induced spikes (<5 spikes)	LTD	Postsynaptic VDCCs	ND	
		RD-induced spikes (>5 spikes)	LTP	Postsynaptic VDCCs	ND	
Rat cerebellum, Purkinje cells	P12–P16	DP	RP	Postsynaptic VDCCs and Ins(1,4,5)P_3-Ca^{2+} stores	↑ $I_{GABA\text{-}A}$ amplitude ↑ mIPSC amplitude	[17–19]
Gerbil lateral superior olive	P7–P12	LFS	LTD	Postsynaptic	ND	[23,24]
Rat nucleus of solitary tract	P17–P36	TS with CNQX and APV	LTP	Presynaptic VDCCs	↑ CV of eIPSC	[25]
Goldfish Mauthner cells	Adult	TS with CNQX and APV	LTP	Postsynaptic	↑ CV of eIPSC	[27–29]
		Sound stimulation		ND	Reveals latent glycinergic connections	

[a]Abbreviations: APV, D-amino-2-5-phosphonovalerate; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CV, coefficient of variation; DNQX, 6,7-dinitroquinozaline-2,3-(1H,4H)-dione, DP, depolarizing pulses; $I_{GABA\text{-}A}$, postsynaptic $GABA_A$-receptor-mediated current; Ins(1,4,5)P_3, inositol (1,4,5)-triphosphate; IPSC, inhibitory postsynaptic current (e, evoked; m, miniature; s, spontaneous; u, unitary); LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; ND, not determined; P, postnatal day; RD, rebound depression; RD, rebound depression; RP, rebound potentiation; Sr^{2+}, strontium; TS, tetanic stimulation; VDCCs, voltage-dependent Ca^{2+} channel. Upward arrows indicate an increase and downward arrows, a decrease.

cells in the deep cerebellar nuclei is a predominant post-inhibitory rebound depolarization and associated spike bursting. In these cells, the number of spikes and the relative amounts of Ca^{2+} that enter the postsynaptic neurons during the post-inhibitory rebound depolarization seem to determine whether LTP or LTD is induced [33]. In the neonatal rat hippocampus, the same conditioning protocol can lead to either LTP or LTD at GABAergic synapses, depending on whether NMDA receptors have been activated during the tetanic stimulation [8] (Fig. 1a). Given that both forms of plasticity require a postsynaptic rise in $[Ca^{2+}]_i$ [8], these observations suggest that the direction of synaptic change is determined by the source of the Ca^{2+} influx: that is, VDCCs for LTP [9], and NMDA channels for LTD [10]. It is not yet clear, however, whether the same GABAergic synapses are able to demonstrate both LTP and LTD. GABAergic synapses are likely to undergo different forms of plasticity depending on their localization along the somatic–dendritic axis [6]. For example, the dendritic localization of NMDA receptors suggests that NMDA-dependent plasticity is likely to occur preferentially at dendritic, rather than at somatic, GABAergic synapses. Future experiments will reveal how interneurons that have been identified anatomically behave in response to the same conditioning protocol.

Long-term plasticity is generated by physiologically relevant stimuli

Much of the interest in long-term plasticity research stems from the possibility that LTP and LTD might be involved in different functions. The relevance of the conditioning protocol to physiological or pathological conditions must, therefore, be taken into account to gain insight into the role of long-term plasticity.

Compelling evidence now suggests that conditioning protocols that are relevant to physiological or pathological situations can induce plasticity at GABAergic and glycinergic synapses. For example, Korn and co-workers have shown that auditory stimulations in goldfish can trigger LTP of inhibitory synapses *in vivo* [29] that shares similar properties with LTP induced by tetanic stimulation [27,28,30]. In the neonatal rat hippocampus, Ca^{2+}-dependent LTP at GABAergic synapses can be

Box 1. Long-term plasticity at inhibitory synapses

When an action potential arrives at the presynaptic terminals, neurotransmitter is released into the synaptic cleft, where it interacts with specific postsynaptic receptors to generate a postsynaptic current. If the amount of neurotransmitter that is released approaches a concentration that saturates the postsynaptic receptors, then the total number and properties of available postsynaptic receptors at the functional synapse will be important limiting factors.

In the adult dentate gyrus, a direct relationship has been found between the number of synaptic $GABA_A$ receptors and the quantal size at potentiated GABAergic synapses in an experimental model of temporal lobe epilepsy [a]. In this model, insertion of new $GABA_A$ receptors underlies the increase in amplitude of unitary inhibitory postsynaptic currents (IPSCs). In addition, blocking clathrin-dependent endocytosis of $GABA_A$ receptors causes a large increase in quantal size in cultured hippocampal cells [b], and insulin can induce a translocation of $GABA_A$ receptors to the surface, thereby increasing the amplitude of miniature IPSCs in cultured neurons [c].

The functional properties of postsynaptic receptors are also crucial for the efficacy of inhibitory synapses. In the CA1 region of the adult hippocampus, high-frequency stimulation induces NMDA-dependent long-term depression (LTD) of GABAergic synapses [d,e]. It has been suggested that this plasticity can be accounted for by a decrease in the efficacy of postsynaptic $GABA_A$ receptors, which is caused by activation of the Ca^{2+}-sensitive phosphatase calcineurin [d,e]. In the cerebellum, the expression of long-term potentiation (LTP) also seems to be a postsynaptic mechanism [f,g] and requires the activation of Ca^{2+}–calmodulin-dependent kinase II and protein kinase A [h]. In the deep cerebellar nuclei, LTD of GABAergic synapses requires the activation of postsynaptic phosphatase activity [i].

Recent experimental evidence indicates that receptor saturation might not occur at all sites of neurotransmitter release [j]. If the concentration of neurotransmitter is not high enough to saturate the postsynaptic receptors, then modifications in the probability of neurotransmitter release or in the number of functional releasing sites might also explain how changes in synaptic efficacy are mediated. These hypotheses are supported by several studies. Thus, long-term plasticity at GABAergic and glycinergic synapses is associated with (1) a modification in the coefficient of variation of evoked IPSCs [k–m], (2) a decrease in the failure probability of unitary IPSCs [k,n], (3) a modification in the frequency of miniature IPSCs with no change in their amplitude [n–p], and (4) a modification in the frequency, but not amplitude, of asynchronous quantal IPSCs evoked in the presence of Sr^{2+} [m].

A modified number of functional neurotransmitter-releasing sites has been demonstrated directly in goldfish [q] and in neonatal rat hippocampus [r]. Modification of the number of functional releasing sites might occur by a mechanism involving either 'all-or-none' clustering and declustering of postsynaptic receptors, or a presynaptic switching on or off of neurotransmitter release. In support of the latter hypothesis, it has been shown that ~30% of postsynaptic $GABA_A$ receptors are associated with nonfunctional presynaptic terminals in hippocampal cultures [s], suggesting the existence of presynaptically silent GABAergic synapses.

If a modification in the probability of neurotransmitter release is involved, then the information should be transmitted back from the postsynaptic cell to the inhibitory presynaptic terminals. In the adult hippocampus, a retrograde messenger released by astrocytes has been shown to participate in long-lasting plasticity at GABAergic synapses [n]. Thus, repetitive firing of a single interneuron leads to an increase in the probability of GABA release by the stimulated interneuron. This effect is caused by the activation of $GABA_B$ receptors on neighbouring astrocytes by GABA released during the repetitive firing on the interneuron. Activation of these receptors leads to a postsynaptic rise in intracellular Ca^{2+} concentration that triggers the release of a retrograde messenger, resulting in an increase in GABA release.

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induced by repeated bursts of action potentials applied at a low frequency to CA3 pyramidal cells [9,12]. This conditioning protocol is related to the sort of activity that neonatal CA3 pyramidal cells might experience *in vivo* through the endogenous bursting properties of these cells [34] or through network-driven synaptic activity that is present at early stages of development [35,36].

The fact that back-propagating action potentials might serve as an associative signal to induce LTP and LTD at neocortical GABAergic synapses [16] strengthens further the idea that physiological stimuli can lead to long-lasting modifications at synapses. Thus, temporally correlated spiking activity in a connected pyramidal cell–interneuron pairing can lead to long-term plasticity at GABAergic

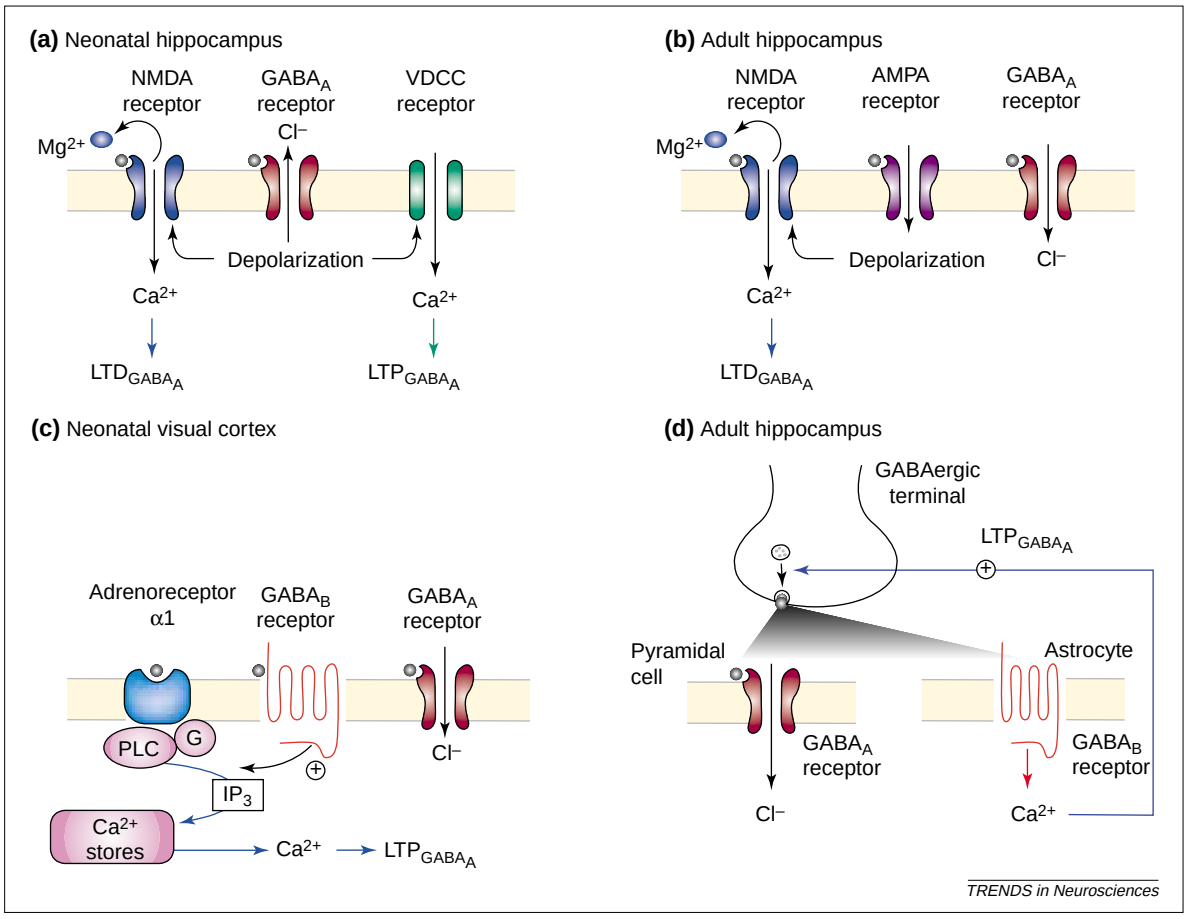

Fig. 1. A postsynaptic rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is required to induce long-term plasticity at GABAergic synapses. (a) In the neonatal rat hippocampus, activation of $GABA_A$ receptors triggers Cl^- efflux and membrane depolarization. This depolarization leads to the activation of voltage-dependent Ca^{2+} channels (VDCC), which results in removal of the Mg^{2+} block from NMDA-receptor channels. Influx of Ca^{2+} through VDCCs leads to long-term potentiation of GABAergic synapses (LTP $GABA_A$), whereas influx of Ca^{2+} through NMDA-receptor channels leads to long-term depression of these synapses (LTD $GABA_A$) [10]. (b) In the adult rat hippocampus, NMDA-dependent LTD can be induced at GABAergic synapses. At this later stage, however, activation of AMPA receptors provides the depolarization that leads to the unblocking of NMDA-receptor channels [7]. (c) In the neonatal rat visual cortex, the rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) relies on the activation of α1 adrenoceptors leading, via G protein (G) and phospholipase C (PLC), to the formation of inositol (1,4,5)-triphosphate (IP_3). This effect is facilitated by the activation of postsynaptic $GABA_B$ receptors [15]. (d) In the adult hippocampus, GABA released from GABAergic terminals activates $GABA_A$ receptors on pyramidal cells, and also $GABA_B$ receptors located on neighbouring astrocytes. Activation of these $GABA_B$ receptors leads to a postsynaptic rise in $[Ca^{2+}]_i$ that triggers the release of a retrograde messenger, probably glutamate, leading to an increase in the probability of GABA release [31].

inhibitory synapses. As reported for transmission at glutamatergic synapses [37,38], the direction of the change in GABAergic synapses depends on the timing between pre- and postsynaptic firing [16].

Functional and pathological relevance of long-term plasticity

Long-term plasticity and behavioural repercussion

Because GABAergic interneurons are involved in the induction and maintenance of behaviourally relevant network oscillations in the adult brain [4,39], one can speculate that long-term plasticity will alter the generation of such rhythms and lead to behavioural modifications. At present, there is no direct evidence in favour of this hypothesis. However, a recent study carried out in the locust olfactory system has shown that synaptic inhibition can change over the course of repeated odour stimulations, with functionally relevant consequences [40]. Although indirect, this study suggests that modifications in inhibitory synaptic strength might alter the patterns of activity generated by a neuronal network, probably leading to behavioural change.

A behavioural consequence of long-term plasticity at glycinergic synapses that impinge onto Mauthner cells has been demonstrated recently in goldfish [29]. Activation of glycinergic interneurons by excitatory synapses of the VIIIth cranial nerve inhibits the contralateral Mauthner cell. Because activation of Mauthner cell system by sound leads to an escape reaction that orients the fish away from the potential predator [41], it was speculated that plasticity at glycinergic synapses [27,28,30] might affect this escape reflex. Thus, LTP was generated at glycinergic synapses *in vivo* by sounds that were below the threshold for escape and delivered at the appropriate frequency [29]. After this conditioning protocol, the probability of escape was, indeed, decreased, whereas the basic properties of the escape reflex were not modified (Fig. 2). The conditioning protocol used in

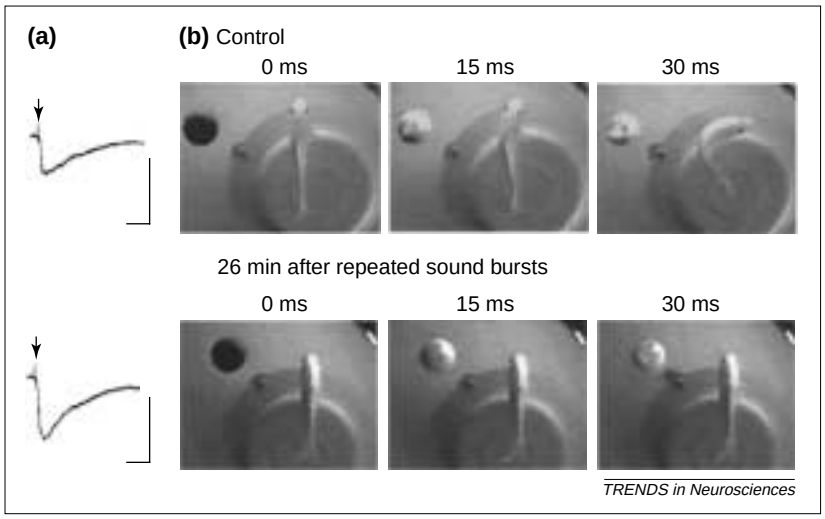

Fig. 2. Behavioural consequence of long-term potentiation at glycinergic synapses. (a) Inhibitory postsynaptic current evoked by stimulation of the VIIIth cranial nerve before (top) and after (bottom) after a four-minute application of repeated sounds. Scale bars, 50 nA, 10 ms. (b) Escape evoked by a falling ball in control (top) and conditioned (bottom) goldfish. Time zero indicates the point at which the ball hit the water. Modified, with permission, from Ref. [29], © (1998) Macmillan Publishers Ltd (www.nature.com/nature).

this study was sufficient to produce LTP of glycinergic synapses but the excitatory inputs onto Mauthner cells were modified only inefficiently [42,43]. In addition, the most effective frequency of sounds that produced the LTP was the one that had the largest effect on behaviour, strengthening further the link between LTP at glycinergic synapses and behavioural modification.

Failure to inhibit GABAergic synapses and epileptogenesis

The first report of long-term plasticity at GABAergic synapse was provided by Stelzer *et al*. [5], who showed that GABAergic synapses also undergo NMDA-dependent LTD after application of repeated electrical stimulations to hippocampal slices [5]. This LTD was thought to contribute, at least in part, to the generation of an epileptiform activity observed after the conditioning protocol. This hypothesis has gained further support from a study by Miles and Wong [44]. Using dual recordings of CA3 pyramidal neurons on hippocampal slices, these researchers showed that recurrent inhibition of GABAergic synapses is reduced after the application of high-frequency stimulation, although they did not identify the site of modification in the inhibitory network. This decrease in efficacy of GABAergic synapses revealed latent polysynaptic excitatory connections and increased the synchronization of excitatory postsynaptic potentials (EPSPs) between the recorded pyramidal cells.

More recently, it has been reported that LTD of GABAergic synaptic transmission can also alter the probability of target neurons firing action potentials. High-frequency stimulation leads to LTP at glutamatergic synapses and increases the ability of the EPSP to trigger an action potential [45]. This increase in EPSP-to-spike coupling seems to be secondary, at least in part, to an NMDA-dependent LTD of inhibitory GABAergic synapses [32]. Therefore, long-term plasticity of inhibitory synapses can affect the output of the target neurons, thereby changing the excitability of neuronal networks.

To understand fully the functional and pathological implications of plasticity at inhibitory synapses, one should consider the heterogeneity of GABAergic interneurons [4]. In the adult hippocampus, different interneurons impinge precisely on specified areas and differentially control the excitability of their target cells. For example, dendritic inhibition controls the generation of Ca^{2+} spikes and shunts excitatory synaptic transmission, whereas somatic inhibition regulates the generation of Na^{+} spikes [46,47]. Thus, to understand completely the overall effect of long-term plasticity at GABAergic synapses on the activity generated by a neuronal network, the interneuron underlying this plasticity should be identified morphologically.

Long-term plasticity and establishing appropriate inhibitory synaptic connections

Several lines of evidence support the idea that spontaneous neuronal activity is necessary for the full development of inhibitory circuitry [48–53]. It is tempting to speculate that the mechanisms involved in developing the inhibitory circuit are similar to those required for long-term plasticity, as has been proposed for excitatory synapses [54–56].

However, the validity of this hypothesis depends on at least two assumptions. First, long-term plasticity should be induced in a restricted period of development that precedes, or corresponds to, the stage of functional synaptic maturation. This has been shown in several developing structures, including the visual cortex [14], hippocampus [8,9] and auditory system [23]. Although the period during which plasticity can be induced differs from one structure to another, it must match closely the crucial window of functional maturation for a specific structure. In the lateral superior olive, the age at which LTD is observed at glycinergic synapses correlates with the period during which inhibitory synapses are eliminated [57]. This suggests that LTD at glycinergic synapses might contribute to the remodelling of inhibitory synaptic pathways, as has been proposed to occur at the neuromuscular junction [54,55]. In the neonatal rat hippocampus, LTP at GABAergic synapses induced by the postsynaptic firing or activation of $GABA_A$ receptors is restricted to the first week of life [8,12], which coincides with the functional maturation of GABAergic synapses [58] (Fig. 3a). This period also coincides with the point at which activation of $GABA_A$ receptors leads to a membrane depolarization and a postsynaptic rise in $[Ca^{2+}]_i$: both processes are required to induce long-term plasticity at GABAergic synapses in the developing hippocampus [9,10]. Second, long-term plasticity should mimic the functional maturation of

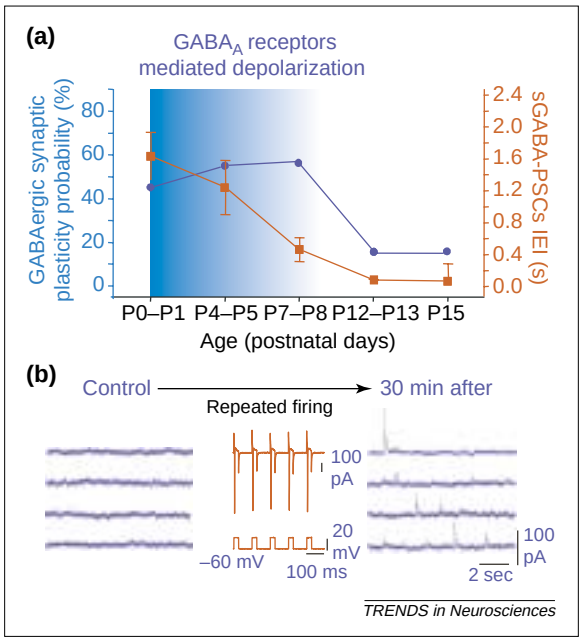

Fig. 3. Long-term plasticity and functional maturation of GABAergic synapses. (a) The probability of triggering long-term potentiation at GABAergic synapses by repeated postsynaptic firing of CA3 pyramidal neurons is restricted to the first week of life in the rat hippocampus (blue graph). This period is concomitant with the functional maturation of GABAergic synapses, as judged by the progressive decrease in the inter-event interval (IEI) of spontaneous GABA-mediated postsynaptic currents (sGABA$_A$-PSCs) (red graph). This period also corresponds with the developmental window in which activation of GABA$_A$ receptors leads to a membrane depolarization (blue shading). Modified, with permission, from Ref. [12]. (b) Repeated postsynaptic firing (20 times, at 0.1 Hz) of a neonatal CA3 pyramidal neurons leads to the appearance of spontaneous sGABA$_A$-PSCs. Reproduced, with permission, from Ref. [12].

inhibitory synapses that occurs *in situ*. At very early stages of development, hippocampal pyramidal neurons are 'silent': that is, they show neither spontaneous nor evoked synaptic activity [59]. On these hippocampal cells, the first functional synapses will be GABAergic [59]. At birth, the conditioning protocol that leads to LTP of GABAergic synapses can induce the appearance of spontaneous GABAergic synaptic activity in previously silent pyramidal cells [12] (Fig. 3b). Thus, the conditioning protocol that leads to LTP can mimic the functional maturation of the GABAergic synapses that occurs in the rat hippocampus [59].

The above observations support the hypothesis that activity-dependent maturation and long-term plasticity are linked, although correlating factors do not demonstrate that the link is causal. Understanding the cellular mechanisms that are involved in both processes will strengthen this link. Neurotrophins are good candidates for common cellular players. For example, activity blockade reduces the number of inhibitory synapses – an effect that is restored by brain derived neurotrophic factor (BDNF) or neurotrophin 4 (NT-4) [52,53]. Neurotrophins can also enhance or reduce inhibitory synaptic transmission [60–63], and a recent study suggests that they are involved in inducing LTD at glycinergic synapses in the developing auditory brain stem [24]. They could, therefore, represent the signal that links long-term plasticity and activity-dependent maturation of inhibitory synapses.

Further experiments that might uncover links between long-term plasticity and the activity-dependent functional maturation and refinement of inhibitory synapses include characterization of the synaptic activity involved in development of inhibitory synaptic connections, and determining whether this activity can induce long-term plasticity at developing synapses.

Conclusion

For a long time, inhibitory synapses have been considered to be important in setting the threshold for synaptic changes at excitatory synapses. The data reviewed here indicate that inhibitory synapses themselves undergo long-term plasticity in different regions of the brain. Not surprisingly, several different mechanisms have been reported to contribute to the induction and persistence of these types of synapse. But, in common with plasticity at excitatory synapses, all forms of plasticity at inhibitory synapses are triggered by a rise in $[Ca^{2+}]_i$. Thus, any conditioning protocol that leads to long-term changes at excitatory synapses is likely to trigger long-term plasticity at inhibitory synapses. In future studies, it will be essential to consider plasticity at both excitatory and inhibitory synapses to understand fully the roles and consequences of activity-dependent plasticity in the development and function of neuronal networks.

Acknowledgements
We thank J. Epsztein and C. Bernard for comments on the manuscript.

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