SYMPOSIUM REPORT

LTP of GABAergic synapses in the ventral tegmental area and beyond

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One of the mechanisms by which the experience-dependent reorganization of neural circuitry can occur is through changes in synaptic strength. Almost every excitatory synapse in the mammalian brain exhibits LTP (long-term potentiation) or LTD (long-term depression), two cellular mechanisms of synaptic plasticity. However, LTP and LTD have been reported much more rarely at fast inhibitory $GABA_A$ receptor synapses. Our recent study suggests that *in vivo* morphine initiates a long-lasting alteration of GABAergic synapses in the ventral tegmental area (VTA) by blocking the mechanisms required for LTP of GABAergic synapses. Here we put this work into the context of other examples of synaptic plasticity at GABAergic synapses.

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The most widely studied candidate mechanisms for changing synaptic strength are LTP and LTD, hypothesized to play critical roles in the establishment of many forms of experience-dependent plasticity, including learning and memory. Recent studies have begun to show that excitatory synapses in brain regions important in addiction can express LTP- and LTD-like changes in response to administration of addictive drugs, and the molecular mechanisms underlying these synaptic modifications share those observed in other forms of plasticity. These findings support the idea that the development of drug addiction, an example of an experience-dependent neuroadaptation, involves usurping or disrupting synaptic plasticity mechanisms (Hyman & Malenka, 2001; Hyman *et al.* 2006; Kauer & Malenka, 2007).

GABAergic synapses exhibit plasticity

By releasing GABA onto $GABA_A$ receptors, inhibitory interneurons control the output of their target neurons by opposing synaptic excitation and limiting the spread of neural activity (Farrant & Nusser, 2005; Akerman & Cline, 2007). As an illustration of this point, blocking $GABA_A$ receptors in the mature CNS increases principal neuron firing rates, and in cortical structures can promote epileptiform bursting. Thus, modifications in the strength of GABAergic synapses will alter the patterns of activity generated by a neuronal network, leading to downstream behavioural changes (Gaiarsa *et al.* 2002). As with plasticity at excitatory synapses, much of the work on LTP and LTD of GABAergic synapses has been carried out in the hippocampus (Stelzer *et al.* 1987, 1994; Grunze *et al.* 1996; McLean *et al.* 1996; Kang *et al.* 1998; Caillard *et al.* 1999*a*,*b*; Lu *et al.* 2000; Gubellini *et al.* 2001, 2005; Chevaleyre & Castillo, 2003; Patenaude *et al.* 2003; Chevaleyre *et al.* 2007). However, synaptic plasticity of GABAergic synapses has also been reported in other brain regions, including the neocortex (Komatsu, 1994; Komatsu & Yoshimura, 2000; Lien *et al.* 2006; Maffei *et al.* 2006), the cerebellum (Kano, 1994; Mitoma *et al.* 1994; Mitoma & Konishi, 1996; Kawaguchi & Hirano, 2002; Saitow *et al.* 2005; Kawaguchi & Hirano, 2007), the deep cerebellar nuclei (DCN) (Morishita & Sastry, 1993, 1996; Aizenman *et al.* 1998; Ouardouz *et al.* 2000), and the brain stem (Glaum & Brooks, 1996; Grabauskas & Bradley, 1999). Our recent work explored the mechanisms underlying synaptic plasticity at GABAergic synapses on midbrain dopamine neurons (Nugent *et al.* 2007).

It is clear that LTP and LTD at GABAergic synapses utilize diverse mechanisms depending on the cell type and developmental stage. As for the majority of forms of excitatory synapse LTP/LTD (Malenka & Bear, 2004), at many GABAergic synapses a rise in postsynaptic Ca^{2+} is necessary to induce plasticity, although the source of Ca^{2+} and the downstream intracellular signalling cascades differ from one brain area to another (Kano, 1995; Gaiarsa *et al.* 2002). Considerable effort has been directed toward

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explaining how activity of inhibitory synapses can generate a rise in intracellular Ca^{2+} when $GABA_A$ receptors are Cl^- channels impermeant to Ca^{2+}.

$GABA_A$ synapses in developing brain

A number of studies in various brain regions have found that Ca^{2+} enters the postsynaptic cell through NMDARs or voltage-gated Ca^{2+} channels (Kano, 1994; Glaum & Brooks, 1996; Grunze *et al.* 1996; McLean *et al.* 1996; Caillard *et al.* 1999*a*,*b*; Lu *et al.* 2000; Ouardouz *et al.* 2000; Nugent *et al.* 2007). For example, early in postnatal development, hippocampal GABAergic synapses can exhibit bi-directional plasticity. In neonates, at this and many synapses, $GABA_A$ receptor-mediated currents are depolarizing, because the expression of specific Cl^- transporters promotes high levels of intracellular Cl^- (Cherubini *et al.* 1991; Akerman & Cline, 2007). The activation of these receptors therefore can provide the initial membrane depolarization required to open NMDAR channels resulting in LTD (Kano, 1994; McLean *et al.* 1996; Caillard *et al.* 1999*b*), or to open voltage-gated calcium channels resulting in LTP at these synapses (McLean *et al.* 1996). This form of LTP at hippocampal synapses is restricted to the first postnatal week, a period when the GABAergic synapses are reaching maturity. At other $GABA_A$ synapses, plasticity is dependent on intracellular sources of Ca^{2+} such as $InsP_3$-sensitive stores, or Ca^{2+}-induced Ca^{2+} release stores (Hashimoto *et al.* 1996; Komatsu, 1996). Several of these examples of $GABA_A$ synapse LTP result from postsynaptic increases in $GABA_A$ receptor number or sensitivity to GABA (Kano, 1994; Ouardouz *et al.* 2000; Maffei *et al.* 2006), although the cellular mechanisms that underlie these changes remain poorly understood.

Postsynaptic electrical activity can trigger LTP of GABAergic synapses

Aizenman *et al.* (1998) studied the cerebellar Purkinje cell-deep cerebellar nuclei synapse and first proposed a novel model to explain how LTP and LTD can be triggered solely by the activity of inhibitory synapses. Here LTP requires a rise in postsynaptic intracellular calcium that can be achieved through rebound depolarization after hyperpolarizing IPSPs. Following a burst of IPSPs, the membrane rapidly depolarizes, reaching a potential at which voltage-gated calcium channels are activated, allowing an essential increase in intracellular Ca^{2+} (Aizenman *et al.* 1998; Ouardouz *et al.* 2000). Again, LTP is apparently maintained by an increase in postsynaptic $GABA_A$ receptor number/conductance, as exogenously applied $GABA_A$ agonists elicit a larger postsynaptic response following LTP induction, but the mechanisms have not been explored further (Ouardouz *et al.* 2000). A form of LTP at GABAergic synapses, recently described in developing visual cortex, is also induced by a novel, postsynaptic activity-dependent mechanism (Maffei *et al.* 2006). This LTP is triggered at GABAergic synapses on star pyramidal cells by subthreshold depolarization of the pyramidal cells during presynaptic firing, but not during coincident presynaptic and postsynaptic firing. The involvement of postsynaptic Ca^{2+} has not been tested as yet, but the rather precise requirements for LTP induction suggest that the signalling molecule involved must operate in a narrow concentration or time window. This form of LTP is also apparently maintained by postsynaptic changes. LTP at these GABAergic synapses may play an important role in the critical period for visual cortex development.

Endocannabinoids mediate LTD of GABAergic synapses

Endocannabinoid-mediated LTD (ec-LTD) at $GABA_A$ synapses in the hippocampus occurs entirely independently of postsynaptic Ca^{2+} (Chevaleyre *et al.* 2006). Ec-LTD is initiated by glutamate release onto the metabotropic glutamate receptors on the postsynaptic cell. Activation of the mGluRs then leads to production of an endocannabinoid, most probably 2-arachidonylglycerol, which acts as a retrograde messenger that binds to CB1 receptors on neighbouring presynaptic GABAergic nerve terminals. CB1 receptors cause a long-lasting depression of GABA release involving PKA signalling and the active zone protein RIM1α (Chevaleyre *et al.* 2007). Thus, unlike many other examples of $GABA_A$ synapse plasticity, ec-LTD is mediated by a change in presynaptic function. Endocannabinoid-mediated LTD has also been observed at other GABAergic and glutamatergic synapses, with some mechanistic variations on the theme (Chevaleyre *et al.* 2006).

$GABA_A$ synapses in the VTA exhibit NO-dependent LTP

Drugs of abuse share one important feature: the activation of the mesolimbic dopamine system. This involves increased firing of dopamine neurons in the VTA and a subsequent increase of dopamine released into the nucleus accumbens and other regions of the limbic forebrain (Di Chiara & Imperato, 1988; Nestler, 2001; Hyman *et al.* 2006). We became interested in the question of whether GABAergic synapses in the VTA could undergo LTP because μ-opioid receptors (the targets of morphine) are concentrated on GABAergic cells, and because GABAergic drugs delivered to the VTA are reinforcing. Using whole-cell recording in rat brain slices, we showed that high-frequency stimulation (HFS)

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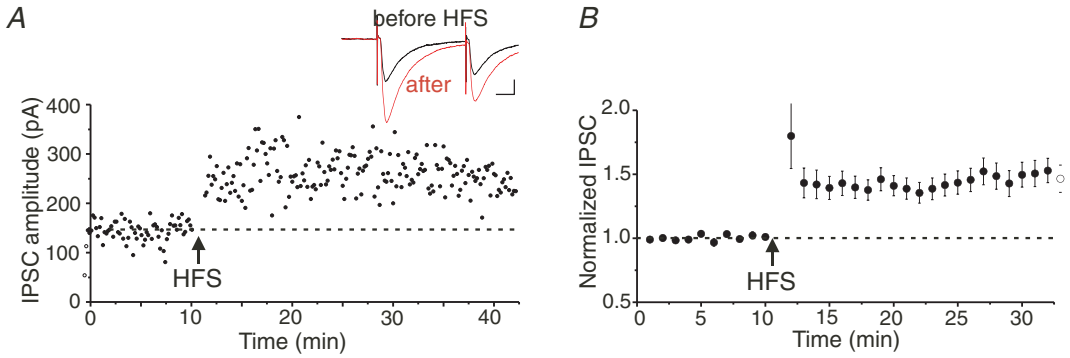

Figure 1. GABAergic synapses on dopamine neurons are potentiated after high-frequency stimulation
A, single experiment showing LTP_{GABA} recorded in a dopamine neuron while whole-cell voltage-clamped at −70 mV. At the arrow (HFS), the afferents were stimulated using a 100 Hz, 1-s-long train, repeated twice 20 s apart, while holding the dopamine neuron in current-clamp. Inset, averaged IPSCs before (black) and 25 min after HFS (red). In this and all figures, 10 consecutive IPSCs from each condition were averaged for illustration. Calibration: 10 ms, 50 pA. In this and all IPSC experiments, 10 μM DNQX and 1 μM strychnine were present to block AMPARs and glycine receptors, respectively. The internal solution was K^+-based, so that IPSCs are seen as inward synaptic currents. *B*, average of 71 experiments from dopamine cells. LTP_{GABA} was not triggered in all cells, but data from all cells are included in this and subsequent graphs. (Adapted from Nugent *et al.* 2007.)

induces LTP of $GABA_A$-mediated synaptic transmission (LTP_{GABA}) onto dopamine neurons of the VTA (Fig. 1) (Nugent *et al.* 2007). LTP_{GABA} required an increase in postsynaptic Ca^{2+} concentration. We found that LTP_{GABA} is heterosynaptic, i.e. it is triggered when glutamate activates NMDA receptors but potentiates neighbouring GABAergic synapses. Importantly, LTP_{GABA} did not require active $GABA_A$ synapses, as the potentiation could be triggered by NMDAR activation in the presence of $GABA_A$ receptor antagonists. LTP_{GABA} was associated with modifications in the coefficient of variation and paired pulse ratio of evoked $GABA_A$ IPSCs, suggesting that it is maintained by persistently increased GABA release. Similarly to ec-LTD, if the LTP induction occurs postsynaptically while the locus of expression is presynaptic, then a retrograde messenger is required that must travel backward from the postsynaptic dopamine neuron to increase GABA release from presynaptic terminals. Several lines of evidence supported nitric oxide (NO) as the retrograde signal maintaining LTP_{GABA}. Inhibition of NO production or bathing the brain slice in NO scavengers blocked LTP_{GABA}. Furthermore, increasing NO levels enhanced $GABA_A$ IPSCs. We also found that a guanylate cyclase inhibitor blocked LTP_{GABA}, whereas a cGMP analogue mimicked it, indicating that NO facilitates GABA release by activation of presynaptic guanylate cyclase (Figs 2 and 4). This was the first demonstration of a presynaptically maintained LTP at GABAergic synapses requiring NO as a retrograde messenger.

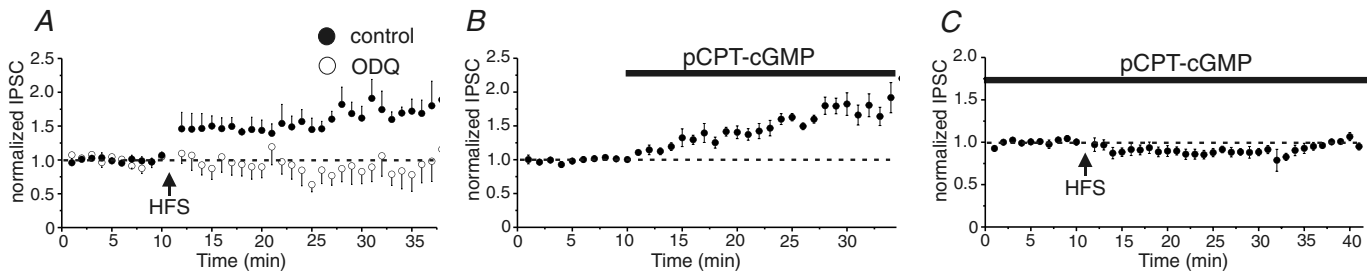

Figure 2. LTP_{GABA} requires NO–cGMP signalling
A, the guanylate cyclase inhibitor ODQ blocks LTP_{GABA}. 10 μM ODQ (1H-[1,2,4] oxadiazolo [4,3-a] quinoxalin-1-dione) was bath-applied beginning at least 10 min prior to HFS (arrow). LTP_{GABA} was blocked, implicating the NO–cGMP signalling cascade in LTP_{GABA} (control LTP: ●, 160 ± 5.7% of pre-HFS values, $n = 6$; ODQ-treated cells: ○, 81 ± 4% of pre-drug HFS, $n = 8$). *B*, pCPT-cGMP (100 μM), a cGMP analogue, potentiated IPSCs without HFS (169 ± 5% of pre-drug values, $n = 11$). *C*, in experiments like those in *B*, after the IPSCs reached a new, potentiated level in 100 μM pCPT-cGMP, HFS was delivered (arrow). pCPT-cGMP occludes potentiation of IPSCs by HFS (89 ± 0.5 of pre-HFS values, $n = 6$). (Adapted from Nugent *et al.* 2007.)

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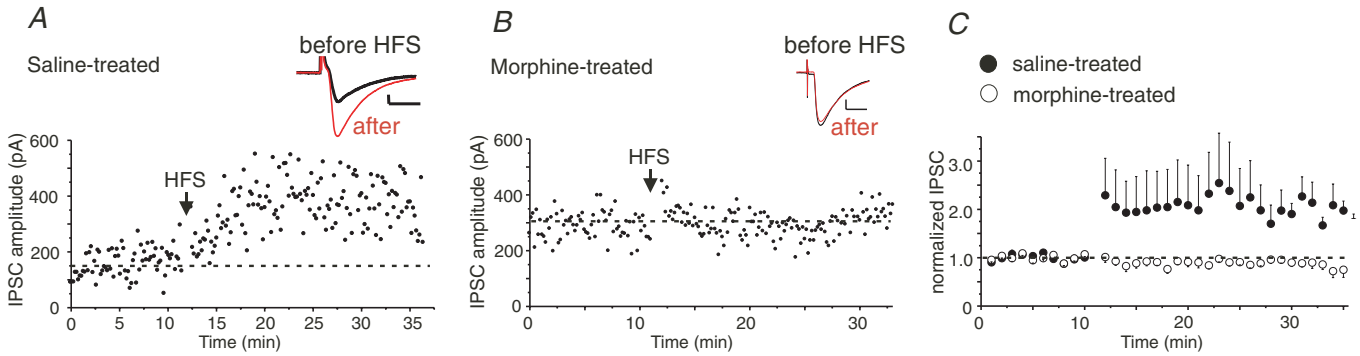

Figure 3. Opioids block LTP_{GABA} *in vivo*
A and *B*, *in vivo* exposure to morphine prevents LTP_{GABA} in slices prepared 24 h later. Single experiments and sample IPSCs (insets) from slices from a saline-injected animal (*A*) and a morphine-injected animal (*B*). Calibration: 10 ms, 50 pA. *C*, averaged experiments from slices prepared 24 h after either saline or 10 mg kg^{-1} morphine injection delivered I.P. (saline cells, ●, 196 ± 20% of pre-HFS values, $n = 10$; morphine-treated cells, ○, 91 ± 4% of pre-HFS values, $n = 11$). (Adapted from Nugent *et al.* 2007.)

NMDA receptor activation on VTA dopamine cells also leads to long-term potentiation of excitatory synapses (Bonci & Malenka, 1999; Overton *et al.* 1999). Our work suggests that NMDAR activation is likely to trigger parallel long-term plasticity at inhibitory synapses. The balance between excitatory and inhibitory synaptic input regulates neuronal cell firing, and therefore activity-dependent simultaneous adjustment of the strengths of inhibitory and excitatory synapses can stabilize the circuit, preventing saturation of neuronal firing (Galarreta & Hestrin, 1998; Varela *et al.* 1999; Abbott & Chance, 2005). Our data suggest that in the VTA, NMDA receptor activation could normally act as a 'gain modulator', with LTP at excitatory synapses balanced by LTP_{GABA}, stabilizing the firing rate of dopamine neurons (Abbott & Chance, 2005). Similarly, in the hippocampus, activity in excitatory afferents can also trigger simultaneous NMDAR-dependent LTP at excitatory synapses and retrograde messenger-induced plasticity at neighbouring inhibitory synapses. However, in the case of endocannabinoid-triggered plasticity, the GABAergic terminals undergo LTD, not LTP. This coincident activation of excitatory and inhibitory synapses in the hippocampus would therefore be expected to do just the opposite of that in the VTA – to synergize, promoting excitability rather than maintaining stability, at least at the local dendritic level. Both ec-LTD in the hippocampus and NO-triggered LTP_{GABA} in the VTA share common features – each is triggered by postsynaptic glutamate receptors, requires a retrograde messenger, and is maintained by persistent presynaptic alteration of GABA release at nearby synaptic terminals – suggesting that these may be common themes in CNS circuit modifications. The precise circuits and circumstances in which synaptic plasticity at excitatory and inhibitory synapses occurs simultaneously will be an exciting avenue for future research.

LTP_{GABA} is blocked by *in vivo* exposure to morphine

NMDA receptor-dependent LTP has been demonstrated at excitatory synapses on midbrain dopamine neurons and

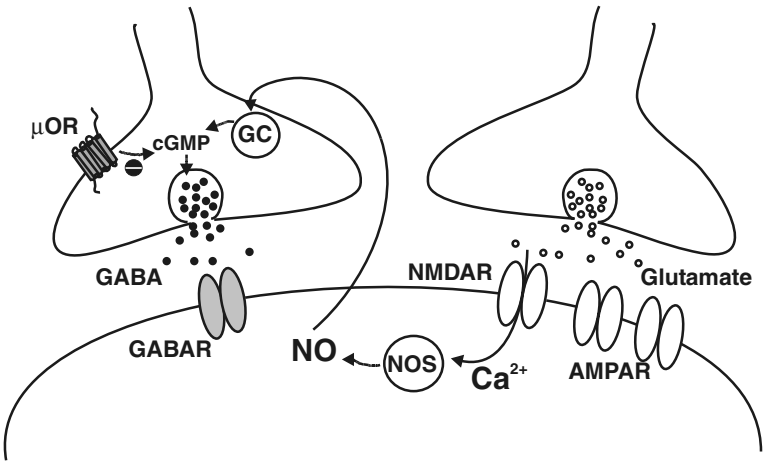

Figure 4. Model of the signalling molecules involved in induction of LTP_{GABA}
LTP of GABAergic synapses is heterosynaptic, triggered by NMDA receptor activation at glutamate synapses and requires NO–cGMP signalling. An *in vivo* injection of morphine prevents LTP_{GABA} through the presynaptic interaction between opioid signalling pathways and NO targets.

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can also be induced by addictive drugs (Bonci & Malenka, 1999; Overton *et al.* 1999; Jones *et al.* 2000; Mansvelder & McGehee, 2000; Ungless *et al.* 2001; Saal *et al.* 2003; Faleiro *et al.* 2004; Liu *et al.* 2005). Several lines of evidence support the involvement of synaptic plasticity at excitatory synapses of the mesolimbic dopaminergic system in the development of addiction (Hyman & Malenka, 2001; Carlezon & Nestler, 2002; Thomas & Malenka, 2003; Jones & Bonci, 2005; Kauer & Malenka, 2007). When we found that LTP_{GABA} accompanies NMDAR activation at VTA synapses, we therefore investigated whether or not morphine, which modulates inhibitory function in the VTA, can modulate LTP_{GABA}. Intriguingly, we found that *in vivo* morphine administration entirely blocked LTP_{GABA} (Nugent *et al.* 2007). $GABA_A$ synapses in VTA slices from rats that had received morphine 24 h earlier did not exhibit LTP (Fig. 3). We further investigated the mechanism by which morphine blocked LTP_{GABA}. Increasing NO levels exogenously had no effect on $GABA_A$ synapses in morphine-treated animals, whereas application of a cGMP analogue still potentiated the synapses. These data suggest a model in which *in vivo* morphine interrupts the signalling between NO and cGMP generation, perhaps at the level of guanylate cyclase (Fig. 4). This key finding may inform the development of novel drugs to prevent or treat addiction.

One question raised by our work is whether other drugs of abuse may also block LTP_{GABA}. Although as yet we have not answered this question directly, intriguing experimental evidence suggests that repeated daily exposure to cocaine *in vivo* reduces $GABA_A$ receptor-mediated inhibition of dopamine neurons (Liu *et al.* 2005). The relationship between LTP_{GABA} and this phenomenon has not yet been tested, but these data suggest that attenuation of local $GABA_A$-mediated inhibition in the VTA may represent a common target of addictive drugs.

Pharmacological blockade of GABAergic transmission, presumably by enhancing Ca^{2+} influx by depolarization or NMDA receptor activation, facilitates the induction of LTP at excitatory synapses. On the basis of this observation, changes in GABAergic synaptic transmission will have important consequences for glutamatergic synaptic plasticity (Chevaleyre *et al.* 2006). The modulation of dopamine transmission in the VTA as a result of the loss of LTP_{GABA} will therefore contribute not only to increased dopamine cell firing and dopamine release, but also to LTP at excitatory synapses, which has been reported after either morphine and cocaine exposure (Ungless *et al.* 2001; Saal *et al.* 2003; Borgland *et al.* 2004; Liu *et al.* 2005). LTP_{GABA} can thus be regarded as contributing to metaplasticity, in which an existing form of synaptic plasticity (LTP at excitatory synapses) is modulated (Abraham & Tate, 2007). After morphine administration the loss of normal inhibitory control coupled with metaplastic potentiation of excitatory synapses may represent neuroadaptations that increase the incentive properties of these addicting drugs.

Conclusions and future directions

Understanding the mechanisms that control plasticity at GABAergic synapses is essential to assessing their critical role in CNS function. Our recent work provides an example of drug-induced modification of GABAergic synapses in response to *in vivo* drug exposure. These findings strengthen the idea that changes in synaptic plasticity may contribute to the development of addictive behaviour. Understanding the cellular mechanisms involved in the particular forms of synaptic plasticity in addiction-related brain areas could provide new insights into the molecular pathology of drug addiction and new therapeutic approaches. Many questions remain to be elucidated regarding how LTP_{GABA} is expressed and maintained at VTA synapses, and whether other drugs of abuse modulate plasticity in the same way that morphine does. Given the importance of NO signalling in the brain, it will also be of great interest to determine whether NO-mediated LTP is a property of GABAergic synapses in other brain areas. Compared with our understanding of synaptic plasticity at excitatory synapses, many questions are unanswered regarding $GABA_A$ synapse plasticity. How are $GABA_A$ receptors trafficked and stabilized during postsynaptically maintained forms of LTP and LTD? How precisely do retrograde messenger molecules persistently modulate GABA release from presynaptic terminals? What are the behavioural correlates of synaptic plasticity at GABAergic synapses, and how long does it last? Why is it that some GABAergic synapses can undergo LTP or LTD while others appear unmodifiable? As patch-clamp recordings have become the standard approach in the study of synaptic function, the use of slices from immature animals has become more common; another important question therefore is to what extent $GABA_A$ synapse plasticity is a feature of immature *versus* mature brain. It is clear that GABAergic inhibition is a key element of essentially every brain circuit, and the control of GABAergic synaptic strength is an important and growing area of interest.

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