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A stabilising influence: Integrins in regulation of synaptic plasticity

Andrew B. McGeachie^a, Lorenzo A. Cingolani^a, and Yukiko Goda^{a,b,*}

^aMedical Research Council Laboratory for Molecular Cell Biology and Cell Biology Unit, University College London, Gower Street, London WC1E 6BT, UK

^bDepartment of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London WC1E 6BT, UK

Abstract

Hebbian synaptic plasticity, such as hippocampal long-term potentiation (LTP), is thought to be important for particular types of learning and memory. It involves changes in the expression and activity of a large array of proteins, including cell adhesion molecules. The integrin class of cell adhesion molecules has been extensively studied in this respect, and appear to have a defined role in consolidating both structural and functional changes brought about by LTP. With the use of integrin inhibitors, it has been possible to identify a critical time window of several minutes after LTP induction for the participation of integrins in LTP. Altering the interactions of integrins with their ligands during this time compromises structural changes involving actin polymerisation and spine enlargement that could be required for accommodating new AMPA receptors (AMPA). After this critical window of structural remodelling and plasticity, integrins “lock-in” and stabilise the morphological changes, conferring the requisite longevity for LTP. Genetic manipulations targeting integrin subtypes have helped identify the specific integrin subunits involved in LTP and correlate alterations in plasticity with behavioural deficits. Moreover, recent studies have implicated integrins in AMPAR trafficking and glycine receptor lateral diffusion, highlighting their multifaceted functions at the synapse.

Keywords

Cell adhesion molecules; Integrin; Hebbian plasticity; LTP; Homeostatic synaptic scaling; Actin

1. Introduction

The activity-dependent modification of synaptic efficacy, termed synaptic plasticity, underpins the capacity of neuronal networks to adapt to changes in external stimuli, and to process and transmit information. Many forms of plasticity have been described, from short-term (ranging from milliseconds to several minutes) (Zucker and Regehr, 2002) to long-term (ranging from hours to years) (Citri and Malenka, 2008), all of which involve changes in synaptic efficacy in a discrete number of synapses. The two most extensively studied forms of long-term plasticity, LTP and long-term depression (LTD), which are thought to represent the cellular correlate of learning and memory, can have different mechanisms of expression depending on the neuronal circuits in which they operate (Citri and Malenka, 2008). Other

forms of plasticity act on a much broader regulatory scale. For example, homeostatic synaptic plasticity serves as a negative feedback mechanism in response to global changes in neuronal network activity, resulting in a compensatory and uniform scaling of all synaptic strengths (Poza and Goda, 2010; Turrigiano, 2008).

The mechanisms by which neurons translate transient changes in stimuli into long-term changes in synaptic efficacy are varied, and can include alterations in presynaptic release probability and postsynaptic responsiveness. Regardless, they usually always involve progressive steps engaging a discrete collection of proteins and signalling events. For example, LTP is commonly divided into two phases: an early phase lasting 1–2 h (E-LTP), which relies on posttranslational modifications and glutamate receptor trafficking, and a later phase (L-LTP), which is dependent on transcription and translation (Abraham and Williams, 2008). Induction of E-LTP requires NMDA receptor (NMDAR) activation and elevation of $[Ca^{2+}]_i$, followed by protein kinase activation, AMPAR phosphorylation and insertion into the postsynaptic membrane; in some cases, E-LTP may also accompany increased presynaptic glutamate release probability. L-LTP appears to entail structural changes requiring local protein synthesis, protease activation and proteolytic cleavage, actin polymerisation and growth of spines, in conjunction with synthesis and insertion of adhesion molecules to stabilise synaptic contacts (Citri and Malenka, 2008; Abraham and Williams, 2008).

Many cell adhesion molecules (CAMs) have a well established role in the development and maintenance of synaptic structures. Moreover, it is now well appreciated that they also have an important role in the activity-dependent functional changes in synaptic efficacy in the mature brain. CAMs that have been demonstrated to play key roles in synaptic plasticity include neuroligins and neuroligins (Dahlhaus et al., 2010), Ephs and ephrins, immunoglobulin superfamily adhesion molecules, cadherins (Dalva et al., 2007) and integrins (Dityatev et al., 2010).

The purpose of this article is to review the literature to date on the regulation of synaptic plasticity by the integrins. This class of CAMs are heterodimers consisting of one of eighteen α and one of eight β subunits, which associate into 24 different combinations, and interact with extracellular matrix proteins or counter receptors on adjacent cells. The integrins are bidirectional, allosteric signalling molecules capable of activating intracellular signalling pathways in response to changes in the extracellular environment (outside-in signalling) or altering cell adhesion as a consequence of intracellularly generated stimuli (inside-out signalling). They have well established roles in a large variety of cellular processes including cell survival, cell proliferation, cell motility, transcription and cytoskeletal organisation (Berrier and Yamada, 2007; Hynes, 2002; Legate et al., 2009). Given their involvement in many basic cellular processes, it is not surprising that most integrin subunits are broadly expressed in many tissues. Although none of the subunits is neural specific, a subset is also expressed in the brain at moderate levels, and a few are enriched at synapses (Table 1). Accumulating evidence suggests that the integrins play important roles in synaptic plasticity, particularly in LTP consolidation (Chan et al., 2003, 2006; Huang et al., 2006; Staubli et al., 1998), albeit other functions have also been described (Charrier et al., 2010; Chavis and Westbrook, 2001; Cingolani and Goda, 2008; Cingolani et al., 2008).

2. Integrins as regulators of Hebbian synaptic plasticity

2.1. RGD peptides

The well established function of integrins in cell–cell and cell–matrix adhesion provided the impetus for investigating whether these CAMs play a role in the synaptic structural changes

associated with LTP (Lee et al., 1980). Early studies made use of peptides containing the Arg-Gly-Asp (RGD) sequence found in extracellular matrix proteins, such as fibronectin, and recognised by many integrin subtypes, including those present in neurons (Ruoslahti, 1996). Application of RGD peptides to acute hippocampal slice preparations compromised LTP, which after an initial robust potentiation, decayed back to baseline levels in 15–30 min, while the baseline transmission was not affected (Staubli et al., 1990). These results provided the first evidence that the integrins targeted by RGD peptides have a role in stabilising LTP. Later studies confirmed these results, illustrating a dose-dependency of RGD peptides and the reversibility of the effects (Xiao et al., 1991). Furthermore, peptides carrying the sequence (Gly-Ala-Val-Ser-Thr-Ala), derived from the fibronectin binding site of integrins, showed the same effects as RGD peptides on LTP stabilisation, indicating that integrin-matrix recognition events are required for the switch of potentiation into a non-decremental state (Bahr et al., 1997). RGD peptides administered 1–10 min after LTP induction also reduced LTP stabilisation, providing further proof that the effects were independent of LTP induction (Bahr et al., 1997; Staubli et al., 1998). If applied 25 min after LTP induction, RGD peptides were however unable to disrupt LTP. Therefore, there appears to be a defined time window of 10–25 min after induction in which integrins are responsible for LTP stabilisation (Staubli et al., 1998). LTP was also disrupted with the disintegrins echistatin and triflavin, RGD containing peptides from snake venom with a much higher affinity to integrins than short synthetic RGD peptides ($K_d \sim 1 \text{ nM}$ – $0.1 \mu\text{M}$) (Chun et al., 2001). As opposed to integrins, NCAM and L1, which belong to the immunoglobulin superfamily of adhesion molecules, are required at an earlier stage of LTP development and stabilisation, because LTP is reduced by compounds that interfere with NCAM and L1 interactions only if used within 10 min from LTP induction (Luthi et al., 1994).

Taken together, the above data are consistent with a model in which integrins are specifically involved in LTP stabilisation. However, recent findings provide a more complex picture. Application of RGD peptides to cultured hippocampal neurons increases the number and length of dendritic spines, while decreasing the number of F-actin clusters (Shi and Ethell, 2006). These effects are partially blocked by function blocking antibodies against integrins (ITG) $\beta 1/\beta 3$, and appear to be mediated by a NMDAR and CaMKII pathway, which is suggestive of a possible role for integrins in the structural changes associated with LTP. Furthermore, the importance of NMDAR and Ca^{2+} signalling in the integrin-dependent spine structural changes is highlighted by the finding that application of RGD peptides increases NMDAR phosphorylation and NMDAR-mediated synaptic responses (Bernard-Trifilo et al., 2005; Lin et al., 2003). Notably, all prior studies that employed RGD peptides in acute slices to investigate the role of integrins in LTP have reported no effects of these peptides on baseline synaptic responses (e.g. Bahr et al., 1997). However, later studies have shown that infusion of the same peptides results in an increase in both the slope and amplitude of AMPAR-dependent postsynaptic potentials (Kramar et al., 2003). The reason for this apparent discrepancy is not clear.

RGD peptides have been valuable in probing the synaptic function of integrins on fast time scales (minutes). However, it is worth-while noting that some studies have reported integrin-independent effects of these compounds. For example, RGD peptides can induce apoptosis by directly binding intracellular pro-caspase-3 (Buckley et al., 1999), and in hippocampal pyramidal neurons, they might increase synaptic NMDAR currents by directly interacting with NMDARs under certain experimental conditions (Cingolani et al., 2008). It is therefore necessary to employ alternative methods, such as function blocking antibodies and genetic manipulations of integrin expression (see below), to validate that integrins are indeed responsible for the synaptic effects of RGD peptides.

2.2. Function blocking antibodies

Several integrin subunits involved in the consolidation of LTP have been identified using function blocking antibodies. Infusion of antibodies against ITG α 5, but not ITG α V or ITG α 2 resulted in a similar decay of LTP as observed with RGD peptides (Chun et al., 2001). Function blocking antibodies were also used to identify specific roles in LTP stabilisation for ITG α 3 (Kramar et al., 2002) and ITG β 1 (Kramar et al., 2006). Although anti-ITG α 3 antibodies induced a small and not statistically significant reduction in LTP levels, subsequent low frequency stimulation could revert LTP more efficiently in slices treated with anti-ITG α 3 antibodies (Kramar et al., 2002). Application of neutralising antibodies against ITG β 1 produced a rapid decline of LTP induced by theta burst stimulation (TBS) to baseline levels within 10–15 min and also prevented TBS-induced actin polymerisation associated with LTP consolidation (Kramar et al., 2006). Collectively, these findings suggest that without α 3 β 1 integrins, LTP remains in some sort of unconsolidated state that is vulnerable to disruption.

2.3. Genetic disruption of integrin function in mice

Mutant mice deficient in the expression of specific integrin subunits have helped to identify which integrins are involved in synaptic plasticity, and importantly, such mice have also provided a means to correlate any effects on LTP with behavioural changes. Single heterozygote mice confirmed a role for ITG α 3, but not ITG α 5 or ITG α 8 in LTP; however, in triple heterozygote mice (ITG α 3/+;ITG α 5/+;ITG α 8/+), LTP was more markedly reduced than in ITG α 3/+ mice (Chan et al., 2003). This suggests that integrin subunits are able to compensate for each other to some degree. Reduced pair-pulse facilitation (PPF) was observed in double ITG α 3/+;ITG α 5/+ and in triple ITG α 3/+;ITG α 5/+;ITG α 8/+ heterozygotes, indicating a possible increase in presynaptic release probability associated with perturbation of α subunit expression. A number of behavioural tests revealed deficits only in triple ITG α 3/+;ITG α 5/+;ITG α 8/+ heterozygous animals: hippocampal-dependent spatial memory was impaired while amygdala-dependent cued and contextual fear conditioning, the latter being also dependent on hippocampal function, were intact. Therefore, a reduction in ITG α 3, ITG α 5 and ITG α 8 expression appears to affect a specific subset of hippocampal processes.

Conditional homozygous knockout of ITG β 1 in CA1 pyramidal neurons of the hippocampus using floxed ITG β 1/CaMKII-cre mice decreased postsynaptic AMPAR responses under basal conditions and LTP, while presynaptic parameters were not affected (Chan et al., 2006). Interestingly, behavioural tests revealed specific deficits in hippocampal-dependent working memory, while spatial memory was unaffected. Although ITG β 1 is likely to be the major subunit for ITG α 3, ITG α 5 and ITG α 8 in the hippocampus (Hynes, 2002), ITG α 3/+;ITG α 5/+;ITG α 8/+ mice showed behavioural deficits (see above) that are different from those of ITG β 1 conditional knockout mice. Such divergent results may reflect the differences arising from global reduction in ITG α 3, ITG α 5 and ITG α 8 versus a more specific ablation of ITG β 1 mainly in CA1 pyramidal neurons.

In another study (Huang et al., 2006), floxed ITG β 1 mice were also crossed with emx1 (empty spiracles homolog 1)-cre mice resulting in an earlier developmental reduction of ITG β 1 in hippocampal neurons (and glial cells) than that obtained with CaMKII-cre mice. This early ablation of ITG β 1 also resulted in LTP deficits. In addition, PPF was increased at short interpulse intervals and the rate of blockade of synaptic NMDAR currents by the open channel blocker MK-801 was delayed, denoting a decrease in release probability. Moreover, the size of the synaptic responses declined more readily during high and low frequency stimulation (HFS and LFS) in ITG β 1 mutants, suggestive of a limited availability of releasable synaptic vesicles or impaired mobilisation of vesicles into the releasable pool in

these mutant mice. Importantly, differences were also observed in the size of NMDAR-mediated responses across a range of stimulation frequencies, which could conceivably account for the observed LTP deficits upon loss of ITG β 1. In contrast, analysis of synaptic transmission in CaMKII-cre;(f) β 1/(f) β 1 mice did not reveal any abnormalities in PPF or in response to HFS; however, deficits were observed with LFS. Because differences in synaptic transmission in response to LFS are generally indicative of changes in the reserve vesicle pool, these data suggest that, in CaMKII-cre;(f) β 1/(f) β 1 mice, the reserve vesicle pool size or alternatively the mobilisation of vesicles from the reserve to the releasable pool, is significantly reduced. As mentioned above, similarly to emx1-cre;(f) β 1/(f) β 1 mice, CaMKII-cre;(f) β 1/(f) β 1 mice also exhibit deficits in LTP, suggesting that the requirement of ITG β 1 for LTP is not secondary to some unspecified developmental role for ITG β 1. Like CaMKII-cre;(f) β 1/(f) β 1 mice, CaMKII-cre;(f) α 3/(f) α 3 mice exhibit deficits in LTP and working memory, but not spatial memory (Chan et al., 2007). In contrast, CaMKII-cre;(f) α 8/(f) α 8 mice do not show any memory deficits (Chan et al., 2010), but still have reduced LTP. These observations seem to suggest differential functions for α 3 β 1 and α 8 β 1 integrins.

2.4. What role do integrins play in LTP?

The limited temporal window of effectiveness of RGD peptides in impairing LTP (Bahr et al., 1997; Staubli et al., 1998), combined with their lack of effect on baseline transmission (but see Kramar et al., 2003) and LTP induction points to the existence of a cryptic RGD binding motif that is only revealed for a short period of time after tetanic stimulation. This is consistent with a role of integrins in stabilising new synaptic structures associated with the transition into long-term consolidation of LTP. Studies using function blocking antibodies or genetic disruption of specific integrin subunits are also consistent with this model, showing a steady decline in LTP after an apparently normal initial potentiation and without effects on baseline synaptic transmission (Table 2). Importantly, integrins have also been shown to drive actin polymerisation after LTP induction, which appears to be necessary for LTP consolidation (Kramar et al., 2006). Collectively, these observations lead to the following proposal for integrin function in LTP: LTP induction results in the disassembly of actin filaments and synaptic adhesive contacts (including those mediated by integrins), which allows for the physical expansion of dendritic spines and the accommodation of new AMPARs into the postsynaptic membrane. This new configuration is then stabilised through integrin-mediated re-assembly of actin networks and adhesive contacts (Fig. 1).

2.5. Different integrins, different roles?

Studies to date provide some evidence that different integrin subunits have distinct roles in synaptic function. Mice heterozygous for the ITG α 3 null allele show deficits in LTP but not PPF (Chan et al., 2003). In contrast, as discussed earlier, α 3/+; α 5/+ mice have deficits in both LTP and PPF, while α 3/+; α 8/+ mice show normal PPF (Chan et al., 2003). This suggests that ITG α 5 may be more involved in some aspects of presynaptic function. Notably, these studies of integrin mutants have involved recordings in hippocampal slices that assess synaptic transmission from a population of synapses from single cells or, in case of extracellular recordings, from population of neurons. Establishing the potential functional specialisations of different integrin subtypes would require a better understanding of how different integrin subtypes are expressed amongst neuronal populations. Moreover, for single cells, it would be important to know whether all synapses express the same complement of integrins; if they are heterogeneously present, then it would be of interest to determine the underlying basis for the differential expression of integrin subtypes at each synapse.

A recent study has provided clear evidence of separate roles for different integrin subunits at individual synapses (Charrier et al., 2010). Inhibition of either ITG β 1 or ITG β 3 with function blocking antibodies has opposing actions on the synaptic dwell time of glycine receptors in cultured spinal cord inhibitory neurons. Whereas antibodies against ITG β 1 make glycine receptors more mobile in and outside synapses, antibodies against ITG β 3 have the peculiar effect to increase glycine receptor mobility at extrasynaptic sites and decrease it at synapses. As a consequence, inhibition of ITG β 1 adhesion reduces the synaptic dwell time of glycine receptors and synaptic glycine currents, whereas inhibition of ITG β 3 adhesion produces the exact opposite effects. Such opposing activities of ITG β 1 and ITG β 3 may be used by neurons to fine-tune inhibitory synaptic tone to modulate network excitability (Charrier et al., 2010). It would be of great interest to identify the physiological extracellular ligands of ITG β 1 and ITG β 3 that function under such conditions.

3. Conclusions and future directions

Integrins have a wide range of roles in a variety of cellular systems (Berrier and Yamada, 2007; Hynes, 2002; Legate et al., 2009). In this review, we have outlined an important function for integrins in regulating the ability of neurons to adjust synaptic strength in response to activity. In particular, we have focused on the role of integrins in Hebbian plasticity, such as LTP. Taken together, it appears that ITG β 1, ITG α 3, ITG α 5 and ITG α 8 all have important roles in the stabilisation of LTP, possibly through the consecutive disassembly and reassembly of adhesive and cytoskeletal elements which may provide a secure new configuration for the long term incorporation of new AMPARs.

Recent work has identified a role for ITG β 3 in another form of synaptic plasticity called homeostatic synaptic scaling, a compensatory mechanism used by neurons to scale up the abundance of synaptic AMPARs in response to chronic activity deprivation (Cingolani and Goda, 2008; Cingolani et al., 2008). It appears that, under basal conditions, ITG β 3 stabilises AMPARs at the postsynaptic membrane as these receptors are selectively endocytosed upon disruption of ITG β 3-ECM interactions. Importantly, neurons lacking ITG β 3 are unable to scale up synaptic AMPARs in response to chronic activity deprivation. These studies provide a first comprehensive description of how integrins regulate AMPAR trafficking and homeostatic synaptic plasticity. It will be of interest to ascertain whether ITG β 3 is also involved in other forms of synaptic plasticity, or whether distinct integrins mediate different types of synaptic plasticity. For example, ITG β 1 could be mainly involved in Hebbian-type plasticity whereas ITG β 3 might play a preferential role in homeostatic plasticity.

In summary, the challenge now is to further define the roles that individual integrins play at synapses. This includes whether separate integrins have distinct functions in different types of plasticity, whether they have specific pre- or postsynaptic roles, and how such cellular functions of integrins may relate to changes in plasticity and behaviour. Moreover, which molecular mechanisms are activated by integrins to bring about these modifications at the level of the individual synapse need to be clarified, as well as the specific ECM alterations that target individual integrins to initiate the changes.

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Fig. 1.

Model of how integrins might consolidate LTP. (A) Synapse immediately after the induction of LTP, showing the presynaptic axon terminal (top, blue) filled with synaptic vesicles, and the postsynaptic compartment (bottom, green) with ionotropic glutamate receptors at the cell surface and actin cytoskeleton, both of which are normally stabilised by integrin interactions with the extracellular matrix. LTP induction results in the disengagement of integrins, and disassembly of both the postsynaptic actin network and ECM. (B) Morphological changes and reassembly after LTP induction: disengagement of integrins, and depolymerisation of the postsynaptic actin network allows for the physical expansion of the postsynaptic compartment (which is associated with a concurrent expansion of the presynaptic terminal), and accommodates the insertion of AMPARs into the postsynaptic membrane. Integrin signalling then controls the polymerisation of the actin cytoskeleton. ECM is reassembled. (C) Consolidation: after a period of instability new integrins are inserted and engage with the ECM to stabilise the new synaptic morphology and function. See text for details. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Localisation of integrin subunits in the hippocampal formation.

Integrin subunit	Pairing with	Cellular localisation	Subcellular localisation	Method	References
$\beta 1$	$\alpha 1-11, \alpha V$	Pyramidal neurons, granule cells, glial cells	Apical dendrites	IHC	Grooms et al. (1993)
				ISH	Pinkstaff et al. (1998)
				ISH	Pinkstaff et al. (1999)
				RT-PCR	Chan et al. (2003)
				IF	Shi and Eithell (2006)
$\beta 3$	$\alpha V, \alpha IIb$	Pyramidal neurons, granule cells	Synaptic	FACS	Cahoy et al. (2008) *
				IF	Chavis and Westbrook (2001)
				RT-PCR	Chan et al. (2003)
				IF, SB	Shi and Eithell (2006)
				IHC	Kang et al. (2008)
$\beta 5$	αV	Pyramidal neurons, glial cells	Synaptic	ISH	Pinkstaff et al. (1999)
				RT-PCR	Chan et al. (2003)
				IF, SB	Shi and Eithell (2006)
				FACS	Cahoy et al. (2008) *
				IHC, SB, EM	Nishimura et al. (1998)
$\alpha 3$	$\beta 1$	Pyramidal neurons	Apical dendrites	FACS	Cahoy et al. (2008) *
				ISH	Pinkstaff et al. (1999)
				RT-PCR, IHC	Chan et al. (2003)
				FACS	Cahoy et al. (2008) *
				ISH	Pinkstaff et al. (1999)
$\alpha 5$	$\beta 1$	Pyramidal neurons, granule cells	Apical dendrites	FACS	Cahoy et al. (2008) *
				ISH	Pinkstaff et al. (1999)
				IHC	Bi et al. (2001)
				RT-PCR	Chan et al. (2003)
				IHC, EM	Einheber et al. (1996)
αV	$\beta 1, \beta 3, \beta 5, \beta 6, \beta 8$	Pyramidal neurons, granule cells, glial cells	Dendrites	ISH	Pinkstaff et al. (1999)
				ISH	Pinkstaff et al. (1999)
				RT-PCR	Chan et al. (2003)
				FACS	Cahoy et al. (2008) *
				IHC	Kang et al. (2008)

IHC = immunohistochemistry, ISH = in situ hybridisation, RT-PCR = reverse transcription polymerase chain reaction, IF = immunofluorescence, SB = subcellular fractionation, FACS = fluorescent-activated cell sorting, EM = electron microscopy

* refers to the full forebrain.

Table 2

Effects of integrin disruption related to Hebbian plasticity.

Integrin	Manipulation	Effects	Unaffected	References
<i>RGD peptides</i>				
RGD	RGDS (1 mM)	↓E-LTP stabilisation (15–30 min to baseline)	Baseline responses, induction	Staubli et al. (1990)
RGD	GRGDSP, RGDS (0.05–10 mM), 60–90 min before TBS	↓E-LTP stabilisation (decays over 40 min), dose-dependency (0.08, 0.35 and 1.0 mM), washout (+90min)	Baseline responses, induction	Xiao et al. (1991)
RGD	GAVSTA (mimics matrix binding domain of RGDS-binding integrins), GRGDSP, RGDS (0.2–1 mM)*	GAVSTA (0.8–1 mM 50–90 min before TBS); ↓E-LTP stabilisation (decays over 40 min), GRGDSP (0.5 mM 1 min after TBS); ↓E-LTP stabilisation (decays over 80–120 min), RGDS (1 mM 10 min after TBS); ↓E-LTP stabilisation (decays over ~60 min)	GAVSTA: baseline responses, postsynaptic burst responses, NMDAR EPSP, GRGDSP: baseline responses	Bahr et al. (1997)
RGD	GRGDSP (0.5–2.0 mM)*	↓E-LTP stabilisation (GRGDSP before 25 min post TBS)	Baseline responses, initial potentiation, postsynaptic burst responses	Staubli et al. (1998)
RGD	GRGDNP ($\beta 1 > \beta 3$, 1 mM), GPenGRGDSPCA ($\beta 3 > \beta 1$, 1 mM), trifluvin (10 μ M), echistatin (1.5, 10 μ M)*	↓E-LTP stabilisation (GRGDNP, GPenGRGDSPCA, echistatin, trifluvin)	Baseline responses	Chun et al. (2001)
<i>Function blocking antibodies</i>				
ITG $\alpha 5$	Anti- $\alpha 2$, $\alpha 5$, αV , $\beta 1$ (non-function blocking) (0.05–0.2 mg/ml)*	↓E-LTP stabilisation (anti- $\alpha 5$)	Baseline responses	Chun et al. (2001)
ITG $\alpha 3$	Anti- $\alpha 3$ (0.2 mg/ml)*	↓E-LTP stabilisation (with 5Hz stim)	Baseline responses	Kramar et al. (2002)
ITG $\beta 1$	Anti- $\beta 1$ (0.2 mg/ml)*	↓E-LTP stabilisation (correlation with actin polymerisation)		Kramar et al. (2006)
ITG $\beta 1$, ITG $\beta 3$	GRGDTP (0.5 mM), anti- $\beta 1$ (10 μ g/ml), anti- $\beta 3$ (10 μ g/ml)	↓ in the GRGDTP induced increase in dendritic spine elongation/number and decreased F-actin cluster number with anti- $\beta 1/\beta 3$ application		Shi and Ethell (2006)
<i>Genetic disruption</i>				
ITG $\alpha 3$, ITG $\alpha 5$ and ITG $\alpha 8$	Single and combined heterozygotes	↓E-LTP stabilisation ($\alpha 3$, $\alpha 3;\alpha 5$, $\alpha 3;\alpha 8$, $\alpha 3;\alpha 5;\alpha 8$) ↓PPF ($\alpha 3;\alpha 5$, $\alpha 3;\alpha 5;\alpha 8$), ↑spatial memory ($\alpha 3;\alpha 5;\alpha 8$)	I/O (ITG $\alpha 3$), cued and contextual fear conditioning ($\alpha 3;\alpha 5;\alpha 8$)	Chan et al. (2003)
ITG $\beta 1$	CaMKII-cre × f($\beta 1$)/f($\beta 1$) mice	↓AMPA transmission, ↓E-LTP	PPF, postsynaptic burst responses,	Chan et al. (2006)

Integrin	Manipulation	Effects	Unaffected	References
ITCβ1	Emx1-cre × f(β1)/f(β1) mice CaMKII-cre × f(β1)/f(β1) mice	stabilisation, ↓ working memory Emx1-cre × f(β1)/f(β1): ↑PPF (short intervals), ↓NMDAR input-output curve, ↓HFS responses, ↓LFS responses, ↓E-LTP stabilisation, CaMKII-cre × f(β1)/f(β1): ↓LFS responses, ↓E-LTP stabilisation	cued and contextual fear conditioning, spatial memory Emx1-cre × f(β1)/f(β1): input-output curve, CaMKII-cre × f(β1)/f(β1): baseline responses, PPF, HFS responses	Huang et al. (2006)
ITCα3	CaMKII-cre × f(α3)/f(α3) mice	↓E-LTP stabilisation, ↓working memory	Input-output curve, PPF, postsynaptic burst responses, mGluR-LTD, spatial memory	Chan et al. (2007)
ITCα8	CaMKII-cre × f(α8)/f(α8) mice	↓E-LTP stabilisation	Input-output curve, PPF, LTD (LFS), spatial memory, working memory	Chan et al. (2010)

* Within manipulation column indicates local pressure injection of compounds. All studies used acute hippocampal slice preparations, except Shi and Ethell (2006) where dissociated hippocampal neurons preparations were studied.