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REVIEW

Integrin activity in neuronal connectivity

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ABSTRACT

The formation of correct synaptic structures and neuronal connections is paramount for normal brain development and a functioning adult brain. The integrin family of cell adhesion receptors and their ligands play essential roles in the control of several processes regulating neuronal connectivity – including neurite outgrowth, the formation and maintenance of synapses, and synaptic plasticity – that are affected in neurodevelopmental disorders, such as autism spectrum disorders (ASDs) and schizophrenia. Many ASD- and schizophrenia-associated genes are linked to alterations in the genetic code of integrins and associated signalling pathways. In non-neuronal cells, crosstalk between integrin-mediated adhesions and the actin cytoskeleton, and the regulation of integrin activity (affinity for extracellular ligands) are widely studied in healthy and pathological settings. In contrast, the roles of integrin-linked pathways in the central nervous system remains less well defined. In this Review, we will provide an overview of the known pathways that are regulated by integrin–ECM interaction in developing neurons and in adult brain. We will also describe recent advances in the identification of mechanisms that regulate integrin activity in neurons, and highlight the interesting emerging links between integrins and neurodevelopment.

KEY WORDS: Integrin activity, Autism spectrum disorder, Schizophrenia, Neurite outgrowth, Synaptogenesis, Synaptic plasticity

Introduction

Proper control of neuronal development and synaptic communication between neurons is critical for normal brain development and function of the central nervous system (CNS). In the developing nervous system, the neural circuitry consists of neuronal networks defined by dendritic processes, axons and synaptic termini. The wiring of the brain (i.e. the formation of neuronal networks) is highly coordinated, and is directed by diverse molecular cascades that ensure neurons proliferate, migrate to the correct locations, extend axons with high spatial and temporal fidelity, and form synaptic connections with appropriate target neurons. Neurite outgrowth and synaptogenesis (synapse formation, function and maintenance) are some of the defining features of early postnatal development, and dysregulation of these processes can lead to impaired neuronal connectivity and increased risk for several neurodevelopmental pathologies, including autism spectrum disorder (ASD) and schizophrenia (Geschwind and Levitt, 2007; McGlashan and Hoffman, 2000).

Numerous studies have investigated the role of the actin cytoskeleton in various aspects of neurobiology. Many actin-regulatory proteins are mutated in neurological disorders, linking cytoskeletal dynamics to normal CNS development and function (Fischer et al., 1998; Joensuu et al., 2018; Sekino et al., 2007). In addition, the extracellular matrix (ECM) and its receptors play key roles as guidance molecules during CNS development, and are implicated in the maintenance of stable neuronal connections and in the regulation of synaptic plasticity (the ability of synapses to strengthen or weaken in response to their activity) (Joensuu et al., 2018; Kerrisk et al., 2014). Although integrins, the main cellular ECM receptors, are widely studied in non-neuronal cells, much less is known about their regulation in the CNS. The identification and functional characterisation of integrin ligands in this tissue has been challenging due to matrix sparsity (Kerrisk et al., 2014). In addition, CNS-specific ECM components, unique integrin co- and counter receptors and crosstalk systems between other neuronal receptors regulate integrin function through mechanisms not applicable to the adhesion, migration and signalling functions of integrins that have been established for non-neuronal cells. Here, we aim to describe some of the known roles of brain integrins in the regulation of neuronal connectivity between CNS neurons. These processes include neurite outgrowth and guidance, formation and maintenance of dendritic spines and synapses, and synaptic plasticity. In addition, we discuss how integrin dysfunction is linked to neurodevelopmental disorders, such as ASD and schizophrenia.

Disrupted neuronal connectivity underlies neurodevelopmental disorders

Dysfunctional neuronal connectivity is thought to emerge during neurodevelopment and to be associated with compromised structural connectivity and aberrant synaptic plasticity (Geschwind and Levitt, 2007; McGlashan and Hoffman, 2000). In particular, two complex neurodevelopmental pathologies, ASD and schizophrenia, are considered to be disorders caused by developmentally reduced synaptic connectivity (Hayashi-Takagi and Sawa, 2010; McGlashan and Hoffman, 2000; Zoghbi and Bear, 2012). The pathophysiology of these disorders has been linked to dysregulation of processes that underlie proper establishment of neural circuits, including neurite outgrowth, guidance and targeting, as well as synaptogenesis and synaptic plasticity (Berretta, 2012; Bourgeron, 2015; Gejman et al., 2010; Joensuu et al., 2018; McFadden and Minshew, 2013; Santangelo and Tsatsanis, 2005; Woo, 2014). Deficits in synapses are of particular interest because reorganisation of circuitry continues at individual synapses throughout life in the form of synaptic plasticity (Sala and Segal, 2014). Interestingly, post-mortem studies have shown that synaptic density is decreased in schizophrenia brains, while in autistic brains there is an increase in glutamatergic synaptic spine density (Hutsler and Zhang, 2010; Moyer et al., 2015). Especially, alterations in the molecular components of the postsynaptic density (PSD) (see Box 1) of dendritic spines are considered as one of the major aetiologies of these disorders (Chen et al., 2014; de Bartolomeis et al., 2014). Despite the fact that ASD and

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Box 1. Structures of synaptic contacts

In addition to neuronal growth cone pathfinding, filopodia-like structures are also the precursors of small membranous protrusions called dendritic spines, which are the postsynaptic regions of most excitatory synapses on dendrites (Harris, 1999; Hering and Sheng, 2001). The dendrites of a single neuron can contain hundreds to thousands of spines. Spines receive synaptic inputs from presynaptic parts of presynaptic terminal, which are the principal sites of excitatory synaptic transmission. Filopodia form contacts with a presynaptic axon terminal, and proper signalling processes promote the stabilisation and enlargement of the filopodium tip into a mature 'mushroom-shaped' dendritic spine. The mature spine consists of a bulbous head and a thin neck that connects the spine head to the dendrite shaft (Ziv and Smith, 1996). As synapses form, the activation of postsynaptic signalling cascades stimulates arbor stability. Conversely, a loss of synaptic inputs leads to dendritic loss. A dendritic spine head typically contains a confined protein-dense region at the postsynaptic membrane of the dendritic spine head, termed the postsynaptic density (PSD), and which is closely apposed to the presynaptic active zone of the axon terminal (Kennedy, 1993). The PSD is a highly organised network of scaffolding proteins, neurotransmitters, receptors, including integrins, and downstream signalling molecules (Levy et al., 2014).

schizophrenia are clinically distinct disorders, both involve deficits in glutamatergic synaptic development and maturation. Understanding how ASD- and schizophrenia-associated genes regulate key cellular pathways in neuronal connectivity, could provide important insights and result in more targeted and efficient ways to treat individual patients.

Integrin activity and signalling in neuronal connectivity and neurodevelopmental disorders

Formation of synaptic connections requires at least three steps: (1) neurite outgrowth and pathfinding, leading to initial recognition of target cells by the axonal growth cone, (2) formation and maturation of synapses, and (3) synaptic stability and plasticity. The coordinated formation of these neural connections requires ECM ligands (e.g. fibronectin, laminin and collagens) and their specific cell adhesion receptors, such as the integrin family (Kerrisk et al., 2014; Park and Goda, 2016) (Box 2; Fig. 1). Integrins are heterodimeric transmembrane receptors, composed of an α- and a β-subunit, and are the main components responsible for cell–ECM interactions and are also involved in cell–cell interactions (Barczyk et al., 2010; Hynes, 2002; Ringer et al., 2017). In humans, 18 α- and 8 β-subunits assemble into 24 integrin heterodimers (Hynes, 2002; Takada et al., 2007). In mammals, the majority of these integrins are expressed in various regions of the brain, such as the hippocampus, cerebellum, thalamus and cortex (Clegg et al., 2003; Pinkstaff et al., 1999). Many integrin subunits are highly expressed in developing neurons (Jones, 1996; Pinkstaff et al., 1999) and some regions of the nervous system maintain expression of integrin subunits, and, in these regions, integrin receptors regulate synaptic stability and plasticity (Jones, 1996; Park and Goda, 2016). Several integrin α- and β-subunits are particularly detected, and highly enriched, in CNS growth cones and synapses (Boxes 1 and 3; Fig. 1) (Park and Goda, 2016; Wu and Reddy, 2012).

Genomic pathway analyses and other gene-centric investigations have revealed that alterations in the genetic code of integrins and other cell adhesion molecules (CAMs), or the proteins mediating CAM signalling, impact on the wiring of neural connections and strongly associate with neurodevelopmental disorders, such as schizophrenia (O'Dushlaine et al., 2011) and ASD (Gilman et al., 2011; Pinto et al., 2010). Accordingly, *in vitro* and *in vivo* studies have implicated integrins, especially the β1 and β3 integrins, as having a role in the developing nervous system through the regulation of processes associated with neuronal connectivity, such as neurite outgrowth and guidance, formation and maintenance of dendrite spines and synapses and synaptic plasticity (Becker et al., 2003; Harper et al., 2010; Z. Huang et al., 2006; Kerrisk et al., 2013; Marchetti et al., 2010; Park and Goda, 2016; Webb et al., 2007). Similarly, in the adult brain, integrins exhibit significant roles in synapse formation and maturation, and furthermore, also regulate synaptic plasticity, which underlies learning and memory (McGeachie et al., 2011).

Several pharmacological and genetic studies have shown a modulatory role for β1 integrins in hippocampal long-term potentiation (LTP) (Babayan et al., 2012; Kerrisk et al., 2014; Staubli et al., 1990) (see Box 4), which is important in the context of

Box 2. Integrin ligands in the CNS

Laminins are high-molecular-mass heterotrimeric proteins composed of an α-, β- and γ-chain. Different laminin isoforms, recognised by α1β1, α2β1, α3β1, α6β1 and α7β1 integrins, regulate axon guidance (Cohen and Johnson, 1991; de Curtis et al., 1991; García-Alonso et al., 1996; Huang et al., 2003; Lentz et al., 1997; Tomaselli et al., 1993). Recently, hippocampal neurons were shown to accumulate a processed form of the laminin α5 chain that is recognised by α3β1 integrin and controls the structural stability of synapses and synaptic transmission (Omar et al., 2017). Fibrous ECM components, such as fibronectin, vitronectin and collagens, are expressed at low levels in the brain, but very little is known about their function in this location (Levy et al., 2014; Omar et al., 2017). Several distinct integrin-interaction sites exist in fibronectin. The arginine-glycine-aspartic acid (RGD) motif recognised by α5β1, α8β1 and the αv-containing integrins (Ruoslahti and Pierschbacher, 1987) and the C-terminal domain of fibronectin (a major heparin-binding region) recognised by α4 integrins (Barkalow and Schwarzbauer, 1991; Sharma et al., 1999) support neurite outgrowth (Humphries et al., 1988). Collagen IV is the major component of basement membranes and promotes neurite outgrowth in an α1β1-driven manner (Lein et al., 1991). Moreover, non-fibril-forming collagens and collagen-like proteins are widely expressed in CNS (Hubert et al., 2009; Humphries et al., 1988; Lein et al., 1991), with some specific forms being expressed by neurons (Fox et al., 2007; Hubert et al., 2009; Sund et al., 2001). The tenascin family of oligomeric glycoproteins, recognised by α7β1, α8β1 and α9β1 integrins, mediate neuron–glia interactions and can exert both inhibitory and stimulatory effects on cell motility (Mercado et al., 2004; Reinhard et al., 2017; Varnum-Finney et al., 1995). Thrombospondins are a family of extracellular matrix proteins, shown to promote neurite outgrowth via α1β1, α3β1 and αvβ1 integrins (DeFreitas et al., 1995; Bamdad et al., 2004; Neugebauer et al., 1991; Charrier et al., 2010). Similarly, vitronectin recognises αvβ1, αvβ3 and αvβ5 integrins, and promotes neurite outgrowth (Felding-Habermann and Cheresh, 1993). Reelin, a secreted ECM glycoprotein, is an integrin-counter receptor, but can also bind to α3β1 integrin and inhibit neuronal migration (Dulabon et al., 2000). Semaphorin 7A, a secreted glycosylphosphatidylinositol-anchored protein, promotes axon growth by interacting with β1 integrin in an RGD-dependent manner (Pasterkamp et al., 2003). Intercellular adhesion molecule-5 (ICAM-5, telencephalin) is a dendrite-specific adhesion molecule that is selectively expressed in the mammalian forebrain and interacts with β1 integrin and regulates the formation of functional synapses (Ning et al., 2013). Chondroitin sulfate proteoglycans (CSPGs) are considered active components of the mature ECM that inhibit functional plasticity in the adult CNS (Orlando et al., 2012). Digestion of CSPGs with chondroitinase ABC in live hippocampal slices promotes the motility of dendritic spines and causes abnormal spine head protrusions. These changes in dendritic spines correlate with β1 integrin activation, suggesting that CSPGs act as integrin ligands at synaptic sites (see Fig. 1).

Journal of Cell Science (2018) 131, jcs212803. doi:10.1242/jcs.212803

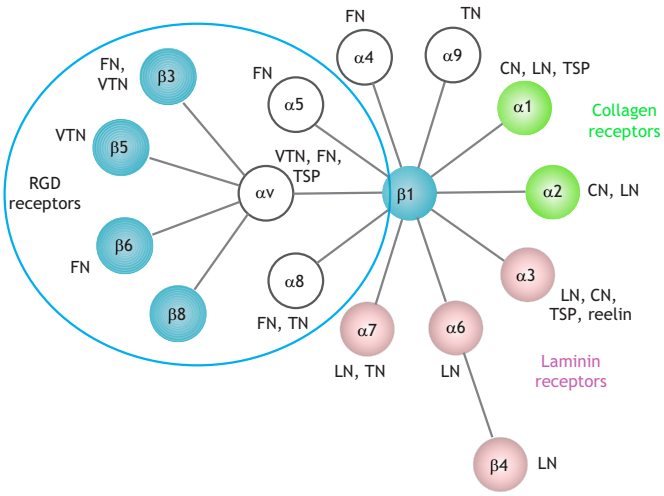

Fig. 1. The brain family of integrin receptors and their ligands. Integrin heterodimers are represented by an α- and a β-subunit connected by a grey line. Laminin receptors are pink; RGD receptors are shown in the blue circle, and collagen receptors are green. β1 integrin is also a receptor for ICAM-5, CSPG and semaphorin 7A. See main text and Box 2 for further details and references. FN, fibronectin; CN, collagen; LN, laminin; TN, tenascin; VTN, vitronectin; TSP, thrombospondin.

ASD, as well as schizophrenia, where LTP defects have been reported in several animal models (Hansel, 2018; Yin et al., 2012). In addition, genetic-linkage studies in population cohorts have identified an association between the *ITGB3* gene, encoding the integrin β3-subunit, and ASD (Carter et al., 2011; Dohn et al., 2017; Napolioni et al., 2011; Schuch et al., 2014). Indeed, mice lacking *Itgb3* exhibit behavioural abnormalities with a strong analogy to ASD in humans, including abnormal social interactions and repetitive behaviour (Carter et al., 2011). *ITGB3* gene variants in humans are also linked to the age of onset in schizophrenia (Wang et al., 2013). Mechanistically, β3 integrin expression regulates the brain serotonin (5-HT) system, a key neurotransmitter pathway. Increases in the expression or the presence of active β3 integrin variants and enhanced integrin signalling to focal adhesion kinase (FAK, also known as PTK2), an important non-receptor tyrosine kinase, modulate the function of the serotonin 5-HT transporter (SERT) and thus increase whole-blood serotonin levels, which have been implicated in developmental abnormalities of ASD (Cook and Leventhal, 1996; Dohn et al., 2017; Jaiswal et al., 2015) and in chronic schizophrenia (DeLisi et al., 1981). Currently, it remains unclear whether β3 integrin contributes to ASD and schizophrenia in its capacity as an adhesion receptor and/or as a cytoskeletal regulator, or whether it serves some kind of adhesion-independent scaffolding function that is distinct to those reported in non-neuronal cells.

Unlike other CAMs, integrins undergo extensive conformational changes that are coupled to their adhesive state (i.e. affinity for ECM ligands). Integrin heterodimers rapidly switch between a bent (inactive) conformation, an extended but not yet ligand-engaged (primed) conformation and a fully extended ligand-engaged (active) conformation (Bouvard et al., 2013; Shattil et al., 2010). Integrin binding to ECM ligands promotes conformational changes within the receptor that favour integrin activation (outside-in signalling). Alternatively, several proteins bound to the intracellular part of integrins regulate receptor conformation and activity state (inside-out activation) (Kim et al., 2011). This conformational flexibility is essential for integrin function in many cell types, especially in platelets and immune cells, but also in adherent cells, such as fibroblasts and epithelial cells (Kim et al., 2011; Shattil et al., 2010). In non-neuronal cells, the main integrin activators at focal adhesions are talin and kindlin (Anthis et al., 2009; Harburger et al., 2009; Ye et al., 2014), while tensins have been recently shown to support integrin activity in fibrillary adhesions (Georgiadou et al., 2017). The importance of integrin activation in the CNS is not well established, even though impaired activation can attenuate synaptic transmission and long-term synaptic plasticity resulting in working memory deficits and the altered behaviour commonly associated with neuronal disorders (McGeachie et al., 2011).

Integrin outside-in signalling triggers the activation of intracellular signalling pathways. The relevance of β1 integrin and its downstream signalling have been primarily studied in hippocampal neurons where it has been shown to signal through the non-receptor tyrosine kinase Arg (also known as Abelson tyrosine protein kinase 2; ABL2) to regulate dendritic branching, synapse plasticity and behaviour in the postnatal mouse hippocampus (Warren et al., 2012). Arg, which is highly expressed in the brain and enriched in dendritic spines (Koleske et al., 1998; Moresco et al., 2005), binds to, and phosphorylates, the intracellular tail of β1 integrin (Simpson et al., 2015) (Fig. 2, point 4). Signalling downstream of β1-integrin–Arg regulates the activity of p190RhoGAP (also known as ARHGAP35) (Bradley et al. 2006), which stabilises dendritic arbors by inactivating RhoA (Sfakianos et al., 2007). Loss of Arg results in several behavioural defects, including impaired hippocampus-dependent learning and memory (Sfakianos et al., 2007). Importantly, a conditional knockout of β1 integrin in the hippocampal excitatory neurons has no apparent effect on the development of dendrites and synapses in mice; however, these animals subsequently exhibit significant reductions in the size and complexity of hippocampal dendritic arbors and loss of hippocampal synapses during late adolescence, resulting in deficits in hippocampus-dependent memory (Warren et al., 2012), a phenotype closely resembling the one described for $Arg^{-/-}$ mice (Moresco et al., 2005; Sfakianos et al., 2007). These findings indicate a role for β1 integrin *in vivo* and describe a role for

Box 3. Key neuronal structures in neurite outgrowth

During development, neurite outgrowth and synapse formation are dynamic and guided processes that mediate the formation of appropriate synaptic connections. At the leading edge of the elongating neurite (dendrite or axon), there exists a highly motile actin- and microtubule-rich structure called the growth cone (named in 1890 by Santiago Ramon y Cajal) that navigates through developing tissues and guides axons and dendrites to their proper target sites (see also Fig. 2). The growth cone is a persistent protrusion with a large number of finger-like actin-rich projections called filopodia and a broad lamellipodium, which are key to growth cone advance and navigation (Gomez and Letourneau, 2014). Proper assembly of the nervous system is based on the ability of growth cones to detect molecular cues in their environment and respond to them by guided outgrowth, a process regulated by CAMs such as the integrin family of adhesion receptors. Point contact adhesions are specialised regions in the growth cone, in which integrins recognise clusters of ECM ligands (Fig. 2). These growth cone adhesion complexes resemble focal adhesions, their non-neuronal counterparts, in that they link integrins to the cytoskeleton to provide traction for growth cone advancement and turning (Kerstein et al., 2015) and recruit adhesion proteins, including talin, paxillin and vinculin (Robles and Gomez, 2006). However, unlike focal adhesions, point contacts typically form within the filopodia, and they are small and transient and under the dynamic control of axon guidance cues (Hines et al., 2010; Renaudin et al., 1999).

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Box 4. Forms of synaptic plasticity

Hebbian or associative synaptic plasticity, the repeated and persistent stimulation of presynaptic cells by postsynaptic cells, induces synaptic transmission in a long-lasting manner via a mechanism that requires NMDA receptors (NMDARs), and has been proposed to play an important role in learning and memory (Brown and Milner, 2003; Lisman, 1989). Long-term potentiation (LTP) synaptic plasticity is another principal cellular mechanism of learning and memory mainly studied in the hippocampus (Citri and Malenka, 2008). LTP is defined by a long-lasting increase in the strength of synaptic transmission between two neurons, which is associated with an increase in the number of synaptic surface AMPA receptors (AMPARs). The LTP requires time to become resistant to disruptions after its formation, a process called LTP consolidation (Lynch et al., 2007). Neuronal networks can adapt to global changes in activity levels through compensatory modifications in the pre- and post-synaptic parameters of synaptic transmission. These forms of synaptic plasticity are known as synaptic homeostasis (Chowdhury and Hell, 2018). Homeostatic regulation of excitability and synaptic efficacy works in conjunction with acutely induced Hebbian plasticity or pathological synapse dysfunction to maintain neuron firing within limits and, thus, preserve stability of brain circuits. Synaptic scaling (or homeostatic scaling), a postsynaptic form of synaptic homeostasis, allows single neurons to regulate their overall action potential firing rate by means of changes in the quantity of AMPA receptors at a postsynaptic site (Chowdhury and Hell, 2018).

the β1-integrin–Arg–p190RhoGAP signalling cascade in protecting against synapse and dendrite loss. Subsequent studies have identified α3β1 as the specific integrin heterodimer that relays Arg-dependent signalling and regulates these late postnatal neuronal functions (Kerrisk et al., 2013).

Integrin inactivation is achieved by proteins that, directly or indirectly, interfere with talin-mediated integrin activation and these include at least SHARPIN, ICAP-1 (also known as ITGB1BP1), filamin and SHANK family proteins (Bouvard et al., 2013; Lilja et al., 2017). Although the specific role of integrin inactivation in the CNS remains to be fully investigated, there are some indications that pathways limiting integrin activity are biologically important. For example, activation of the EphA4 receptor tyrosine kinase, a member of the largest family of Ephrin (Eph) receptor tyrosine kinases, by its ligand ephrinA3 promotes spine shortening partially by inhibiting β1 integrin-induced spine elongation (Fig. 2, point 5) (Bourgin et al., 2007). Intriguingly, SHARPIN was identified as being a scaffold protein of the PSD (Lim et al., 2001), even though its role in regulating integrin activity in the synapse has not been studied. In addition, we recently reported that the scaffolding proteins SHANK1 and SHANK3, which organise large protein complexes in the PSD of excitatory synapses (Sheng and Kim, 2000) and participate in growth cone motility in developing neurons (Durand et al., 2012), inhibit β1 integrin activity in cancer cells and neurons (Fig. 2, point 7) (Lilja et al., 2017). The N-terminal Ras-association domain of SHANK3 binds to active GTP-bound Rap1 (Rap1A and Rap1B proteins), which are known integrin activators, and counteracts Rap1–RIAM–talin-mediated β1 integrin activation in growth cones of mouse cortical neurons derived from *Shank3αβ*$^{-/-}$ mutant mice (lacking the α and β isoforms of SHANK3), as well as significantly reducing Rap1-driven filopodia formation in rat hippocampal neurons. Importantly, these functions were disrupted by ASD-associated *SHANK3* mutations (Lilja et al., 2017). While many open questions remain with regard to the role of integrin activity in neurons, these data suggest that the pathways that regulate integrin activity can be shared between non-neuronal cells, immune cells and neurons.

Integrin–ECM interactions in axonal outgrowth and pathfinding

A significant element of neural development is defined by the exceptional ability of neurons to extend growing axons over long distances and to navigate these axons to specific destinations to form synapses (Chen and Cheng, 2009). Although many aspects of these processes remain unclear, the importance of the growth cone, a highly motile structure at the growing end of a developing axon, is undisputed. Growth cones, which are in contact with the ECM, contain adhesions that are called point contacts (see Box 3). These adhesions are particularly evident in growth cone filopodia and are dependent on integrin–ECM engagement (Myers et al., 2011). The complexity of integrin–ECM interactions has been extensively studied in non-neuronal tissues (Humphries et al., 2006), whereas the identification and characterisation of ECM ligands for neuronal integrins in the CNS has been less comprehensive (Kerrisk et al., 2014). Nevertheless, many ECM ligands (e.g. laminin, fibronectin, collagen, vitronectin and tenascin) have been described to mediate CNS functions through distinct integrins (Myers et al., 2011) (see Box 2). In non-neuronal cells, integrins signal across the plasma membrane to activate non-receptor tyrosine kinase and small GTPase-dependent signalling, as well as to mechanically couple the ECM to the actin cytoskeleton through adaptor proteins, such as talin and vinculin (Harburger and Calderwood, 2009). Similar, yet distinct, mechanisms have also been described in advancing growth cones. Here, integrin binding to the ECM triggers integrin activation and clustering in point contacts (see Box 3), and the recruitment of proteins, such as talin and vinculin, to the integrin cytoplasmic tails (Fig. 2, point 6), thereby linking adhesions to the cytoskeleton. Thus, the ECM provides mechanical support for growth cone adhesion and enables traction forces (the amount of the total traction that is parallel to the direction of motion) to stabilise leading edge protrusions (Kerstein et al., 2015). In addition, key adhesion-localised kinases, such as FAK and Src, are activated, thereby initiating adhesion-induced signalling, which reciprocally regulates adhesion assembly and turnover (Fig. 2, point 6) (Kerstein et al., 2015; Robles et al., 2005; Robles and Gomez, 2006).

In addition, FAK and Src kinases serve as integration points for signals generated by integrins and growth factors. FAK and Src are activated downstream of neuronal growth factor (NGF), and FAK-mediated upregulation of integrin receptor expression is necessary for NGF-induced enhancement of axon growth from dorsal root ganglions (DRGs) (Tucker et al., 2005, 2008). Members of the Ras and Rho family of small GTPases have also been implicated in various steps of neurite outgrowth. In growth cones, the Rho GTPase family members Rac1 and RhoA regulate specific aspects related to the assembly and maturation of point contacts downstream of integrin signalling. Rac1 promotes the assembly of transient point contacts, whereas RhoA is necessary for the stabilisation of existing point contacts (Woo and Gomez, 2006). R-Ras, another Ras GTPase family member, is necessary for integrin-mediated neurite outgrowth, presumably owing to its ability to activate phosphatidylinositol 3-kinase (PI3K) signalling (Oinuma et al., 2007). Small GTPases have also been implicated in mediating growth-cone-modulatory signals downstream of the Eph receptors, either by activating R-Ras and Rap1A (in case of EphB2 receptor), or by inactivating Rap1 (EphA4 receptor) (Hall and Lalli, 2010). Both R-Ras and Rap1 are known to enhance integrin activity and cell spreading in non-neuronal cells (Arthur et al., 2004; Zhang et al., 1996); however, the links between these GTPases in growth cone guidance and regulation of integrin activity and matrix adhesion are not fully consolidated.

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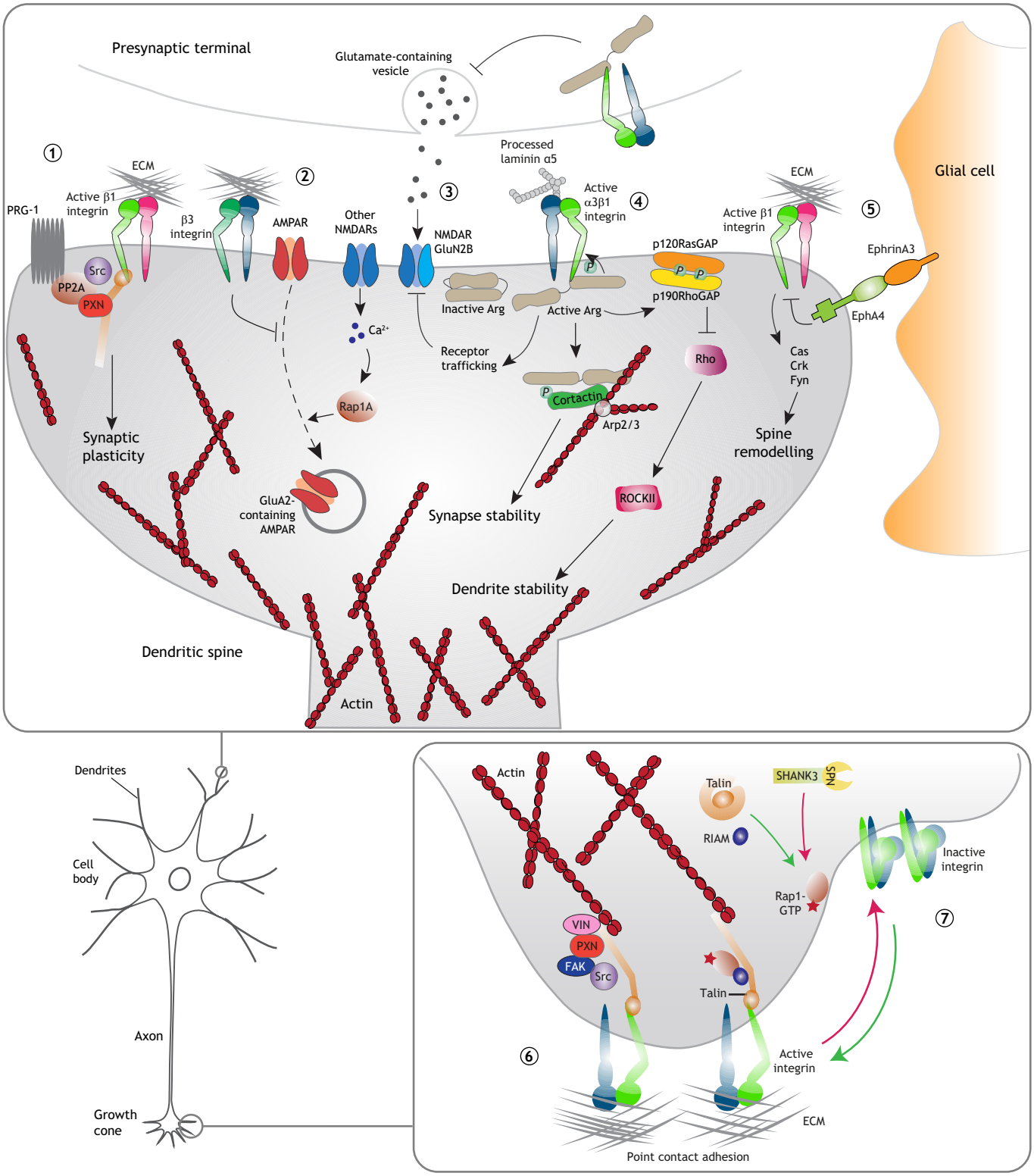

Fig. 2. See next page for legend.

Growth cones use integrins to select between trajectories offered by different ECM molecules. Several studies have reported that integrins interact with numerous guidance molecules, such as netrins (Lemons et al., 2013), semaphorins (Pasterkamp et al., 2003), slit proteins (Stevens and Jacobs, 2002) and ephrins (Bourgin et al., 2007), which are known to serve as attractive or repellent cues during the establishment of neuronal connections. Integrins and axon guidance molecules have been suggested to function together through three different paradigms. First, integrins serve as receptors for axon guidance molecules, such as netrin-1 and semaphorin 7A (Lemons et al., 2013; Pasterkamp et al., 2003). Semaphorin 7A contains an RGD-integrin-binding motif and enhances axon outgrowth by

Fig. 2. Role of integrin activation in growth cone and synapse regulation. Integrins exert several distinct roles in dendritic spines and at growth cone point contacts. (1) Integrin activation by its co-receptors. In hippocampus, PRG-1 directly interacts with PP2A and modulates its phosphatase activity at the PSD. This molecular interaction leads to recruitment of the adhesion molecules Src, paxillin and talin following activation of β1 integrins, which then controls the regulation of spine density and LTP. (2) Integrins and receptor trafficking. Integrin β3 stabilises AMPAR at the postsynaptic membrane by inhibiting AMPAR trafficking, a process requiring basal NMDAR activity, Ca^{2+} influx and activation of the small GTPase Rap1A. (3) NMDAR receptors (consisting of the ubiquitous GluN1 subunit and a variable composition of the GluN2A–GluN2D, and GluN3A or GluN3B subunits) coordinate synapse stability and plasticity. Integrin–Arg signalling normally reduces GluN2B-dependent NMDAR currents by regulating receptor trafficking pathways and the probability of any presynaptic neurotransmitter release. (4) The β1-integrin–Arg–p190RhoGAP signalling cascade. A proteolytically processed laminin α5 chain engages and activates integrin α3β1 to activate downstream signalling. Upon α3β1 activation, Arg binds to the integrin β1 tail, resulting in its activation. Arg-mediated phosphorylation of the integrin β1 tail provides a second binding interface for Arg and is required for further phosphorylation. Arg phosphorylates downstream substrates, including p190RhoGAP and cortactin. Phosphorylated p190RhoGAP allows for complex formation with p120RasGAP [Ras p21 protein activator (GTPase-activating protein) 1, also known as RASA1] at the postsynaptic membrane, which inhibits RhoA GTPase activity and promotes dendrite stability. Arg also phosphorylates and binds to cortactin, thereby promoting the nucleation and stabilisation of F-actin by the Arp2/3 complex, which ultimately promotes the stability of dendritic spines. (5) Integrins at the neuron–glia contact. Activation of EphA4 by glial ephrinA3 inhibits integrin activation and downstream signalling and regulates spine remodelling. (6) ECM-induced integrin activation and adhesion-induced signalling. Contact with ECM triggers integrin activation and downstream signalling by recruiting talin, paxillin (PXN) and vinculin (VIN) and activating FAK and Src, which are essential for the formation of growth cone protrusions. (7) SHANK-mediated integrin inactivation. Rap1 binds RIAM on the plasma membrane triggering talin recruitment and activation to adopt an open conformation. Talin binds to the integrin β-subunit cytoplasmic tail propelling integrins towards the extended active conformation and facilitating their coupling to the actin cytoskeleton. SHANKs bind to, and sequester, active GTP-bound Rap1, and so diminish β1 integrin activation through the Rap1–RIAM–talin complex. See main text for further details and references.

binding to β1 integrin and promoting integrin activation and integrin-dependent MAPK signalling (Pasterkamp et al., 2003). Second, signals from axon guidance receptors, such as semaphorin 3 or Eph receptors, are dependent on integrin engagement (Kullander and Klein, 2002; Schlomann et al., 2009). Semaphorin 3A promotes the extension of hippocampal dendrites through integrin-dependent phosphorylation of FAK (Schlomann et al., 2009). Defects in the formation of dendritic arbors have been observed in the hippocampus of semaphorin 3A-knockout (*Sema3a*$^{-/-}$) mice and in cultures of *Sema3a*$^{-/-}$ neurons (Schlomann et al., 2009). Furthermore, inactivation of β1 integrin or ablation of FAK blocks semaphorin 3A-induced assembly of integrin-mediated adhesions and extension of dendrites in hippocampal neurons. Finally, integrin signalling has been proposed to converge with signals emanating from axon guidance receptors, such as semaphorin 3, Slit and Eph receptors, to coordinate neurite guidance (Nakamoto et al., 2004).

Integrins in synaptogenesis and synapse maturation

In addition to their central role in controlling neurite outgrowth and guidance, integrins and the ECM are also crucial regulators of synaptogenesis (Ethell and Pasquale, 2005). Synaptogenesis is an important developmental process involving synapse formation, synapse maintenance and activity-dependent synapse refinement and elimination (Cohen-Cory, 2002). Several integrin subtypes expressed in the brain are enriched at synapses, where they predominantly localise within the PSD (see Box 1); here, the β1 subunit pairs with various α-subunits including α3, α5, α8 and αv, whereas the β3 subunit is only found together with the αv subunit (Park and Goda, 2016).

Studies using neuronal cultures and animal models have shown that α3 and α5 integrin subunits coupled with the β1 integrin subunit are involved in the regulation of excitatory synaptogenesis in the hippocampus. For instance, in response to synaptic stimulation with glutamate, α5 integrin is targeted to synapses (Webb et al., 2007) where it regulates spine morphogenesis and synapse formation. Depletion of α5 integrin in hippocampal neurons impedes the formation of dendritic protrusions, spines and synapses. The α5 integrin-mediated synapse formation pathway might be regulated by mechanisms that are dependent on Src kinase, Rac and the adaptor protein G protein-coupled receptor kinase interacting protein 1 (GIT1), as alterations in the activity of these molecules also significantly decreases the number of spines and synapses (Webb et al., 2007). Similarly, the inhibition of β1 integrin results in a decreased number of synapses in the apical dendrites of CA1 pyramidal neurons (Nikonenko et al., 2003).

In the developing brain, dendritic spines show highly dynamic behaviour that is thought to facilitate the formation of new synaptic contacts (Lippman and Dunaevsky, 2005). Indeed, several studies indicate integrins in regulation of dendritic spine morphogenesis, a process whereby dendritic spines change their shape and size (e.g. filopodia-like dendritic protrusions of immature neurons are replaced by dendritic spines in more mature neurons). In primary hippocampal cultures, activation of β1 and β3 integrins by RGD-motif-containing integrin-binding peptide induces dendritic spine elongation and formation of new filopodia, processes that can be attenuated by treatment with integrin function-blocking antibodies or the *N*-methyl-D-aspartate receptor (NMDAR) antagonist (Shi and Ethell, 2006). Mechanistically, this involves integrin-dependent control of spine remodelling through NMDAR/CaMKII-dependent actin reorganisation. Accordingly, the expression of constitutively active α5 integrin leads to an increased number of filopodia-like protrusions (Webb et al., 2007).

Similarly, indirect regulation of integrin activity alters spine morphology. For example, overexpression of autoactivating matrix metalloproteinase 9 (MMP-9) promotes β1 integrin activation, which contributes to the thinning and elongation of spines (Michaluk et al., 2009). Moreover, integrins are critical in the maintenance of neuron–glia contacts, and the β1 integrins have been shown to induce glia-dependent excitatory synaptogenesis in hippocampus (Hama et al., 2004). The integrins have been implicated as effectors of EphA4–ephrinA3 signalling at the neuron–glia interface and regulation of spine morphogenesis and synaptic plasticity (Fig. 2, point 5). The EphA4 receptor is enriched in dendritic spines of adult hippocampal neurons, whereas its ligand ephrinA3 localises to glia cells that are in close contact with spines (Carmona et al., 2009; Murai et al., 2003). Activation of EphA4 by ephrinA3 in hippocampal slices inhibits integrin function by triggering disassembly of integrin signalling complexes [consisting of Crk-associated substrate (Cas; also known as BCAR1), FAK and proline-rich tyrosine kinase 2 (Pyk2; also known as PTK2B)], which act to stabilise dendritic spines and modulate synaptic interactions with the extracellular environment (Bourgin et al., 2007).

NMDARs along with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) drive excitatory glutamatergic transmission and maintain the substantial synaptic plasticity detected at excitatory synapses (Chan et al., 2006; Shi and Ethell, 2006). During the late stages of synaptic development, integrins have been shown to be necessary for maturation of

excitatory hippocampal synapses. The β1 integrins, together with Arg kinase, normally support a reduction in neurotransmitter release in the presynaptic portion and alter the postsynaptic NMDAR composition from GluN2B- to GluN2A-containing receptors, properties that define mature synapses, by regulating receptor trafficking pathways (Xiao et al., 2016) (Fig. 2, point 3). The loss of integrin-regulated Arg kinase allows for high levels of neurotransmitter release and GluN2B-enriched immature-like synapses to be maintained throughout late postnatal development and early adulthood; this causes enhanced NMDAR-mediated currents, overall dendritic spine loss and altered NMDAR-dependent long-term synaptic stability and plasticity (Xiao et al., 2016).

Integrins in synaptic plasticity

Spines are the principal sites of excitatory synaptic transmission, playing important roles in synaptic plasticity and memory formation (Sala and Segal, 2014). Synaptic plasticity, meaning activity-dependent changes of synaptic efficacy, underpins the ability of neuronal networks to respond to changes in external stimuli and transmit information. This involves structural and functional reorganisation of neuronal networks. Multiple forms of plasticity have been described from acting over the short term (ranging from milliseconds to several minutes) (Zucker and Regehr, 2002) to over the long term (ranging from hours to years) (Citri and Malenka, 2008) (see Box 4). In addition to integrins being structurally important in synapse formation, accumulating evidence suggests that integrins, in general, are critical for multiple forms of plasticity (Chan et al., 2003).

In adulthood, most dendrite branches and many dendritic spines are stable for extended periods of time (Ethell and Pasquale, 2005), which is important for proper brain function. Nevertheless, dendritic spines retain some dynamic properties in the adult brain and can change in response to certain forms of plasticity (LTP; a principal cellular mechanism for learning and memory) (see Box 4) (Carlisle and Kennedy, 2005; Yuste and Bonhoeffer, 2001). Pharmacological and genetic approaches indicate that inhibition or deletion of integrins, such as α3, α5 or β1 integrin, or their ligands (Chun et al., 2001, 2006, 2007; Huang et al., 2006; Kramár et al., 2002, 2006; Staubli et al., 1990), or of integrin-associated kinases such as FAK and Src (Bernard-Trifilo et al., 2005; Huang et al., 2001; Yang et al., 2003), significantly abrogates cytoskeletal organisation in synapses and impairs LTP and presynaptic release probability in the hippocampus, resulting in defects in spatial memory (Babayan et al., 2012; Huang et al., 2006; Kerrisk et al., 2013; Staubli et al., 1990). Mice with genetically reduced expression of α3 or β1 integrin subunits show impaired hippocampal LTP and deficits in hippocampal-dependent working memory tasks (Chan et al., 2006, 2007; Huang et al., 2006). This strongly suggests that α3 integrin is the functional binding partner of the β1 subunit that is involved in synaptic plasticity and behaviour. Interestingly, mice with postnatal forebrain and excitatory neuron-specific knockout of α8 integrin demonstrate LTP dysfunction specifically at Schaffer collateral–CA1 synapses, while displaying normal behaviour in multiple hippocampal-dependent learning tasks (Chan et al., 2010) for which other integrin subunits, such as α3 and β1 integrin, are required. Taken together, these findings suggest that, although the absence of several integrin subunits can lead to impaired LTP, different integrin receptors have distinct roles in modulating behavioural functions.

The process of LTP requires spine stabilisation that is mediated either by rapid cytoskeletal alterations (Kramár et al., 2006; Lynch et al., 2007; Rex et al., 2009) or by delayed changes in protein synthesis (Bramham, 2008) (see Box 4). LTP induction in the adult hippocampus with naturalistic theta-burst stimulation (TBS) triggers rapid and persistent actin polymerisation in individual dendritic spines (Lin et al., 2005), which is known to be required for maintenance of potentiation (Lynch et al., 2007). Inhibition of β1 integrins with antibodies soon after LTP stimulation prevents this actin polymerisation (Kramár et al., 2006) and interferes with LTP consolidation in a similar way to what is seen upon the treatment with actin polymerisation inhibitors (Ackermann and Matus, 2003; Fukazawa et al., 2003). Thus, the initial stages of consolidation appear to involve the integrin-driven regulation of the cytoskeleton, which is similar to what occurs in situations in which non-neuronal cells undergo rapid morphological changes. Additional studies have identified a further integrin-dependent stabilisation step in LTP, occurring between the rapid and late phases of consolidation (Babayan et al., 2012). The initial TBS-induced burst of actin polymerisation and integrin activation is followed by a phase that is non-responsive to adhesion with slow recovery of the β1 integrin pool. Treatment of animals with a β1 integrin-blocking antibody specifically during this recovery phase, but not at later stages, appears to effectively block long-term object location memory (Babayan et al., 2012). Thus, dynamic regulation of β1 integrins modulates LTP via multiple mechanisms.

Integrins also cooperate with other postsynaptic regulators of spine plasticity. For instance, postsynaptic plasticity-related gene 1 (PRG-1; also known as PLPPR4), previously shown to control lysophosphatidic acid (LPA) signalling at glutamatergic synapses (Trimbuch et al., 2009), has recently been demonstrated to regulate spine density and synaptic plasticity through protein phosphatase 2A (PP2A) and β1 integrin activation (Liu et al., 2016) (Fig. 2, point 1). Interestingly, PRG-1-expressing cells display an increased surface expression of active β1 integrin and enhanced binding to the β1 integrin-specific ECM substrates fibronectin and laminin, but not to collagens, tenascin or vitronectin (Liu et al., 2016). These findings are in line with the increase seen in spine numbers in PRG-1-overexpressing neurons and support the notion that PRG-1 is involved in mediating structural plasticity (Liu et al., 2016). Accordingly, PRG-1 deficiency in mice is associated with a reduction in spine numbers and β1 integrin activity, and is reported to alter LTP and impair spatial memory (Liu et al., 2016).

Another form of synaptic plasticity, homeostatic synaptic plasticity, serves as a negative feedback mechanism in response to global changes in neuronal network activity, resulting in compensatory scaling of all synaptic strengths (Pozo and Goda, 2010) (see Box 4). Integrin β3 regulates excitatory synaptic strength and has been shown to mediate homeostatic plasticity and to be specifically required for a postsynaptic form of synaptic homeostasis, termed synaptic scaling (see Box 4), in both dissociated cultures and organotypic slices (Cingolani et al., 2008). In hippocampal pyramidal neurons, β3 integrins possess a unique ability to stabilise synaptic AMPARs. The inhibition of the interaction between β3 integrin and its ligand results in decreased excitatory synaptic currents by inducing the endocytosis of GluA2-containing AMPARs via Rap1 signalling (Cingolani et al., 2008) (Fig. 2, point 2). The overexpression of β3 integrins produces substantial changes in the abundance and composition of synaptic AMPARs without affecting dendritic spine structure. In addition, ablation of β3 integrin prevented the homeostatic scaling up of AMPARs upon chronic activity suppression (see Box 4) (Cingolani et al., 2008; Cingolani and Goda, 2008). Conversely, another form of synaptic homeostasis, which involves changes in presynaptic content, occurs independently of β3 integrin (Cingolani et al.,

2008). In hippocampal slices, the loss of β3 integrin activity did not compromise Hebbian forms of plasticity (see Box 4), and neither acute pharmacological disruption of β3 integrin–ligand interactions nor genetic deletion of *ITGB3* appears to alter LTP. In contrast, acutely disrupting ligand-induced β1 integrin activation or genetic deletion of *ITGB1* selectively interferes with LTP stabilisation (Kramár et al., 2006; Babayan et al., 2012). These findings show that there is less requirement for ITGB3 than ITGB1 during LTP, and suggest differential roles for these two integrins in supporting hippocampal circuit functions.

Conclusions and perspectives

Integrins and their ECM ligands are widely expressed in the CNS where, to a certain degree, they exert highly specialised and often multifaceted roles. Activation or genetic depletion of integrins result in variable neuronal phenotypes, depending on the developmental stage of ablation and the specific cell types or CNS structures targeted. This not only underscores the central role of integrins in neuronal systems, but also the complexity of the processes they regulate. Integrin crosstalk with other receptor systems appears to be a recurrent regulatory mechanism for neuronal function. In addition, signalling pathways that emanate from the cytoplasmic domains of integrins and the subsequent activation of downstream non-receptor tyrosine kinases, such as FAK, Src and, importantly, Arg, are essential for integrin-regulated processes in the development and normal function of neuronal networks. However, there are many questions that remain. Apart from a few scattered reports addressing this issue, the importance of the regulation of integrin activity in neurons is poorly understood. Given the critical role of the actin cytoskeleton, ECM ligands and the dynamic crosstalk between integrins and other neuronal receptors, it is likely that integrin activity is under tight spatio-temporal control. Determining the mechanisms that control integrin activity in neurons and understanding the similarities or unique features of these processes compared to those identified in non-neuronal cells will be a major future challenge. In addition, it will be important to determine whether mutations in integrins or their effectors and adaptor proteins are linked to neurological disorders. In the past decade, integrins have emerged as essential mechanotransducers in cancer cells, stem cells and fibroblasts, regulating important stiffness-guided processes, including durotaxis and mechanosensitive gene expression and differentiation (Ringer et al., 2017). As mechanosensing was recently shown to be critical for axon guidance (Koser et al., 2016), it will be interesting to investigate the role of integrins in signalling of mechanosensitive cues during nervous system development. Finally, endosomal trafficking of integrins in non-neuronal cells is critically important to generate subcellular polarisation and clustering of integrins, especially in migrating cells (De Franceschi et al., 2015). Currently, it is largely unknown whether similar integrin trafficking routes also function in the developing nervous system to support neuronal structures, including growth cones. Integrins and their downstream signalling pathways are implicated in numerous pathological conditions, and a broad range of antagonists against integrin emanating pathways have been developed. Given the multifaceted and significant functions of integrins in the brain, it is possible that these receptors could also represent important therapeutic targets in specific neurological disorders.

Acknowledgements

We apologise to all colleagues whose work was not mentioned here due to space limitations. We thank H. Hamidi for editing the manuscript prior to submission.

Competing interests

The authors declare no competing or financial interests.

Funding

The author's laboratory was supported by funding from the Academy of Finland, an European Research Council Consolidator Grant, the Sigrid Juséliuksen Säätiö (Sigrid Juselius Foundation) and Syöpäjärjestöt (the Cancer Society of Finland). J.L. is supported by the Turku Doctoral Programme of Molecular Medicine (TuDMM) and Suomen Aivosäätiö (Brain Society of Finland).

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