Neuroscience and Biobehavioral Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Dysregulation of group-I metabotropic glutamate (mGlu) receptor mediated signalling in disorders associated with Intellectual Disability and Autism

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ARTICLE INFO

Article history:
Received 5 September 2013
Received in revised form 13 January 2014
Accepted 6 February 2014

Keywords:
Synaptic plasticity
Developmental disorders
Mental retardation
Fragile X
Fmrp
TSC
PTEN
Neuroligin
Homer
SHANK
SAPAP3

ABSTRACT

Activation of group-I metabotropic glutamate receptors, mGlu1 and mGlu5, triggers a variety of signalling pathways in neurons and glial cells, which are differently implicated in synaptic plasticity. The earliest and much of key studies discovered abnormal mGlu5 receptor function in Fragile X syndrome (FXS) mouse models which then motivated more recent work that finds mGlu5 receptor dysfunction in related disorders such as intellectual disability (ID), obsessive-compulsive disorder (OCD) and autism. Therefore, mGlu1/5 receptor dysfunction may represent a common aetiology of these complex diseases. Furthermore, many studies have focused on dysregulation of mGlu5 signalling to synaptic protein synthesis. However, emerging evidence finds abnormal mGlu5 receptor interactions with its scaffolding proteins in FXS which results in mGlu5 receptor dysfunction and phenotypes independent of signalling to protein synthesis. Finally, both an increased and reduced mGlu5 functioning seem to be associated with ID and autism spectrum disorders, with important consequences for potential treatment of these developmental disorders.

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http://dx.doi.org/10.1016/j.neubiorev.2014.02.003
0149-7634/

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1. Introduction

Metabotropic glutamate (mGlu) receptors are key players in excitatory transmission and important regulators of synaptic plasticity. Accumulating evidence over the past 15 years has implicated abnormal expression, signalling and function of group-I metabotropic glutamate (mGlu) receptors in the pathophysiology of neurodevelopmental disorders which has led to ongoing Phase IIB clinical trials targeting mGlu receptors in patients affected by one of these disorders, *i.e.* Fragile X syndrome (FXS).

mGlu receptors are members of class C G-protein-coupled receptor (GPCR) superfamily and consist of eight receptor subtypes, which can be subdivided into three groups on the basis of sequence homology, pharmacology and G-protein coupling specificity (reviewed by Nicoletti et al., 2011). Group-I includes the mGlu1 and mGlu5 receptor subtypes, which are coupled to G_{q11} proteins. Their activation stimulates phospholipase C-mediated phosphatidylinositol-4,5-bisphosphate (PtdIns-4,5-P_2) hydrolysis with ensuing formation of inositol-1,3,4-trisphosphate ($InsP_3$) and diacylglycerol (DAG), which, in turn, activate intracellular Ca^{2+} release and protein kinase C (PKC), respectively (reviewed in Hermans and Challiss, 2001). There are several splice variants of mGlu1 and mGlu5 receptors, of which mGlu1a, mGlu5a and mGlu5b are characterized by a long C-terminus intracellular domain interacting with scaffolding proteins (see below). Group-II and -III include mGlu2 and mGlu3, and mGlu4, mGlu6, mGlu7 and mGlu8 receptor subtypes, which are all coupled to $G_{i/o}$ proteins. Their activation negatively regulates adenylyl cyclase activity and voltage-sensitive Ca^{2+} channels. While mGlu1 and -5 receptors are generally found in the peripheral portions of postsynaptic densities, mGlu2, -3, -4, -7, and -8 receptors are mainly (but not exclusively) localized on pre-synaptic terminals, where they negatively regulate neurotransmitter release (reviewed by Nicoletti et al., 2011 and Niswender and Conn, 2010).

The present review focuses on group-I mGlu receptor-mediated signalling pathways and their potential role in mechanisms underlying Intellectual Disability (ID). Pivotal work in the Fmr1 knockout (KO) mouse modelling FXS first linked group-I mGlu receptors with ID- and autism-related disorders. Several excellent reviews have been published over the years on altered group-I mGlu receptor signalling and dendritic protein synthesis in FXS (Bassell and Warren, 2008; Bhakar et al., 2012; Dölen et al., 2010; Krueger and Bear, 2011; Waung and Huber, 2009). We will highlight the early FXS work to provide an historical backdrop to the motivation of more recent work. In particular, we will focus on group-I mGlu receptor signalling pathways implicated in synaptic plasticity and cognitive functions, and their modulation by associated post-synaptic proteins. We will also discuss the possible implication of group-I mGlu receptor dysfunctions in the pathophysiology of different disorders associated with ID and autism, based on recent results on mouse models mimicking mutations in genes related to these pathologies, such as TSC, PTEN, SHANK3, and NLG-3. Recent work on the involvement of mGlu5 receptor signalling in obsessive compulsive disorder (OCD) will also be discussed.

2. Group-I mGlu receptors

2.1. Structure, distribution and signal transduction pathways: an overview

mGlu1 and mGlu5 receptors contain (i) a large NH_2 extracellular portion containing a Venus fly trap (VFT) glutamate binding domain and a cysteine-rich domain, (ii) seven transmembrane α-helices (TMD), and (iii) an intracellular COOH terminal portion, which is the site of interaction with several bridging and regulatory proteins (Fig. 1). Similarly to the other mGlu receptor subtypes, mGlu1 and mGlu5 receptors form functional homodimers stabilized by an intersubunit disulphide bridge and require two molecules of orthosteric agonists (such as glutamate) for full activation (Kniazeff et al., 2004; Pin et al., 2005). Recent studies carried out in heterologous expression systems have shown that mGlu receptors can also form intra-group heterodimers (*e.g.*, mGlu1 with mGlu5 receptors), adding further complexity to the mode of action and mechanisms of regulation of group-I mGlu receptors (Doumazane et al., 2011). According to the current model of mGlu receptor activation, glutamate binding to one VFT induces a conformational modification of the transmembrane domains which stabilizes the dimer in an active conformation with a resulting activation of G proteins (Gomeza et al., 1996; Pin et al., 1995). However, group-I mGlu receptors with long C-terminal regions, *i.e.* mGlu1a, mGlu5a, and mGlu5b receptors, can also display constitutive activity. This results from the spontaneous formation of an active TMD conformation, independent of agonist binding (Goudet et al., 2005).

mGlu1 and mGlu5 receptors show different regional and developmental expression profiles. mGlu5a receptor expression and functional coupling to polyphosphoinositide hydrolysis is elevated in forebrain regions during the first three postnatal weeks and declines afterwards, whereas expression of mGlu1 receptors in the cerebellum increases with age and is maximal in adulthood (reviewed in Catania et al., 2007). Both mGlu1 and mGlu5 receptors are present in cortical and hippocampal interneurons (van Hooft et al., 2000) where they interact with NMDA receptors in regulating neural oscillations and brain connectivity. mGlu5 receptors are also found in astrocytes, and their function is up-regulated during the process of reactive gliosis (reviewed by D'Antoni et al., 2008). Group-I mGlu receptors are mainly localized post-synaptically (Romano et al., 1996; Shigemoto et al., 1997), although a pre-synaptic localization of these receptors has also been described (Gereau and Conn, 1995; Thomas et al., 2000). In dendritic spines, mGlu1 and mGlu5 receptors are typically localized in the perisynaptic region, and can therefore be recruited by the high levels of glutamate that are released during sustained synaptic transmission (Baude et al., 1993; Nusser et al.,

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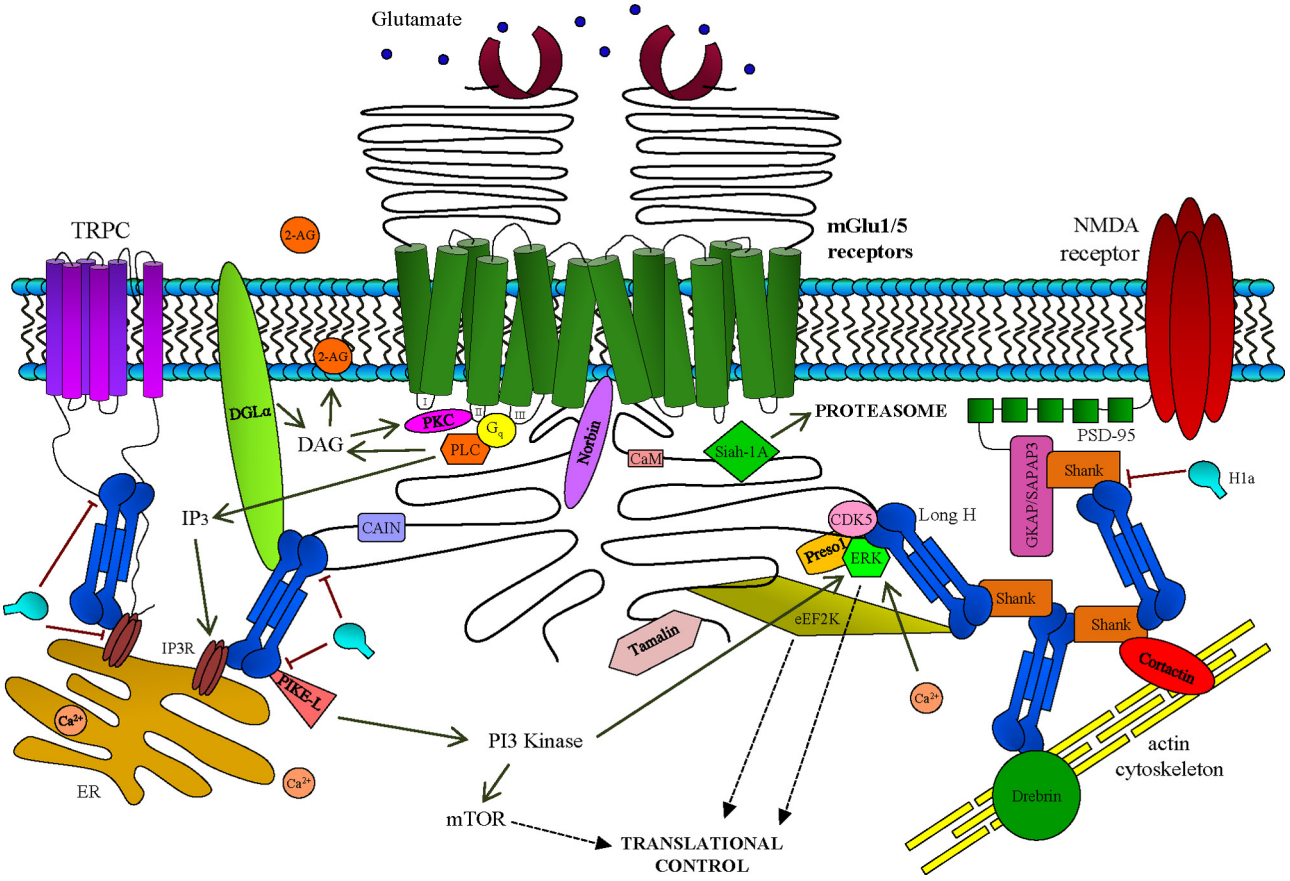

Fig. 1. Schematic representation of proteins that interact directly or indirectly with mGlu1/5 receptors and mediate receptor signalling. The COOH terminal intracellular domain of group-I mGlu receptors interacts with Norbin, Calmodulin (CaM), Siah-1A, Calcineurin inhibitor protein (CAIN), Tamalin, and long (Long H) and short isoforms (H1a) of Homer proteins. Homer proteins interact through their amino-terminal domain with IP3 receptors, Shank, PIKE-L, drebrin, and the transient receptor potential channel (TRPC). Homer interactions with other proteins such as ryanodine receptors, oligophrenin 1, dynamin III, Rho small GTPases are not depicted here. The association Homer-IP3R couples IP3R to mGlu1/5 receptors and mediates intracellular Ca^{2+} signalling. Long H proteins regulate the TRPC channel function by mediating the formation of the TRPC/Homer/IP3R complex. The mGlu5 receptor-dependent activation of PI3K pathway is mediated by the association between Long H and PIKE-L. Shank-Homer interactions associate mGlu1/5 receptors to NMDA receptors through PSD95 and GKAP, and anchor mGlu/NMDA complex to the actin cytoskeleton through Cortactin and Drebrin. mGlu5/Homer binding is regulated by Preso1 (see text for details). Long H proteins bind the diacylglycerol lipase-alpha (DGLα) that converts DAG into 2-AG. The short Homer 1a (H1a), acting as a dominant negative modulator, competitively binds the target proteins of Long H such as mGlu1/5, PIKE-L, Shank, TRPC, IP3R. mGlu5 receptors also associate with eEF2K either directly or indirectly through Homer proteins. Activation of mGlu5 receptors exerts a tight control on protein synthesis through mechanisms involving mTOR and ERK pathways, and regulation of eEF2K activity (see text).

1994; Vidnyanszky et al., 1996). Interestingly, mGlu1/5 receptors are also found at extrasynaptic sites with a higher frequency of mGlu5 than mGlu1 receptors (Lujan et al., 1997). mGlu5 receptors have also been detected in cell nuclei where they stimulate PtdIns-4,5-P_2 hydrolysis and generate nuclear $InsP_3$ (Kumar et al., 2008; O'Malley et al., 2003). Interestingly, activation of these nuclear mGlu5 receptors induces a different set of genes as compared to the activation of surface mGlu5 receptors (Jong et al., 2009).

In addition to polyphosphoinositide hydrolysis, activation of mGlu1/5 receptors is also linked to other signal transduction mechanisms, such as mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) (Peavy and Conn, 1998), phospholipase D (Holler et al., 1993), phospholipase A2 (Dumuis et al., 1993), phosphoinositide 3-kinase (PI3K) (Rong et al., 2003), mammalian target of rapamycin (mTOR) (Hou and Klann, 2004) and formation of the endocannabinoid, 2-arachidonoylglicerol (2-AG) (Jung et al., 2005). Activation of ERK and mTOR by group-I mGlu receptors is linked to *de novo* protein synthesis in neurons, a process that underlies long-term changes in activity-dependent synaptic plasticity (reviewed in Waung and Huber, 2009).

2.2. *mGlu1/5 signalling pathways are modulated by associated post-synaptic proteins*

mGlu1/5 receptor-mediated signalling is modulated by several mechanisms, including the interaction with regulatory proteins at the intracellular C-terminal receptor domain (Fig. 1 for a schematic representation). A distal proline-rich region of the C-terminus domain of mGlu1a and mGlu5a/b receptors interacts with members of the Homer family proteins, which function as scaffolds between receptors and a number of post-synaptic adaptor and signalling proteins (reviewed by Shiraishi-Yamaguchi and Furuichi, 2007). The Homer protein family includes long and short isoforms (Homer 1b, -1c, -2 and -3; and Homer 1a, respectively). All isoforms share a highly conserved N-terminal EVH1 [enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) homology 1] domain, which interacts with proline-rich sequences present in mGlu1a and mGlu5 receptors, and in

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a variety of signalling, adaptor, or cytoskeletal proteins, such as the InsP3 receptors, ryanodine receptors, Shank, transient receptor channels (TRPC), the phosphatidylinositol-3-kinase enhancer (PIKE), dynamin III, drebrin, oligophrenin-1 and diacylglycerol lipase-alpha (DGLα) (Feng et al., 2002; Gray et al., 2003; Jung et al., 2007; Kammermeier et al., 2000; Kim et al., 2006; Rong et al., 2003; Tu et al., 1998, 1999; Yuan et al., 2003). Remarkably, most of these proteins play a role in group-I mGlu receptor-mediated long-term depression (LTD) (Asrar and Jia, 2013; Chae et al., 2012; Fujii et al., 2010; Holbro et al., 2009; Nadif Kasri et al., 2011; Sharma et al., 2010; Taufiq et al., 2005). The EVH1 domain is also required for binding the eukaryotic elongation factor 2 (eEF2) kinase (eEF2K), which regulates the elongation step of translation (Park et al., 2008). Long Homer isotypes have a coiled-coil C-terminal domain that mediates formation of homotetramers linking mGlu1a and mGlu5 receptors to postsynaptic proteins (Brakeman et al., 1997; Hayashi et al., 2006; Kato et al., 1998; Xiao et al., 1998). The short Homer1a, which lacks the coiled-coil domain, cannot form dimers, is induced in response to sustained synaptic activity and acts as a dominant negative modulator of mGlu receptor signalling by disrupting protein-to-protein interactions mediated by long Homer (Kammermeier and Worley, 2007; Xiao et al., 1998). Long Homers also interact with Rho family GTPase proteins, namely Cdc42, through their C-terminal region (Shiraishi et al., 1999). An additional mechanism regulating mGlu5 receptor-Homer interaction involves Preso1, a protein which binds both Homer and mGlu5 receptors and facilitates phosphorylation of mGlu5 receptors in the Homer binding domain by recruiting type-5 cyclin-dependent kinase (CDK5) and ERK (Hu et al., 2012; Orlando et al., 2009) (Fig. 1).

Interaction with Homer proteins controls several functions of mGlu1/5 receptors such as the constitutive activity of mGlu5 receptors (Ango et al., 2001), mGlu5 receptor trafficking and lateral mobility (Ango et al., 2001; Coutinho et al., 2001; Sergé et al., 2002), mGlu5 receptor coupling to ion channels (Kammermeier et al., 2000), as well as coupling to signalling pathways such as the ERK, PI3K, the DGLα/endocannabinoid system (Jung et al., 2007; Mao et al., 2005; Ronesi and Huber, 2008; Rong et al., 2003), and eEF2K (Park et al., 2008). mGlu5 receptor/Homer interactions are also able to modulate NMDA receptor function although the underlying mechanisms have only been partially elucidated. mGlu5 receptors are physically linked to the NR2 subunit of the NMDA receptor channels through a chain of anchoring proteins including postsynaptic density protein 95 (PSD-95), guanylate kinase-associated proteins (GKAPs), Shank, and Homer (Tu et al., 1999). The Homer-Shank complex is organized to form a mesh-like flexible matrix structure, with Homer forming an antiparallel tetramer which exposes a pair of N-terminal EVH1 domains able to interact with other proteins (Hayashi et al., 2009) (Fig. 1). The mGlu1/5 receptor-mediated facilitation of NMDA receptor activity described in several experimental paradigms (reviewed in Field et al., 2011), may tightly depend on the stability of the mGlu/Homer/Shank complex. Interestingly, activation of both mGlu1 and mGlu5 receptors has been shown to inhibit NMDA receptor function when the mGlu/Homer/NMDA receptor complex is disrupted (Bertaso et al., 2010; Moutin et al., 2012).

The C-terminus domain of group-I mGlu receptors interacts with tamalin (Kitano et al., 2002), norbin (Wang et al., 2009) and the calcineurin inhibitor protein (Ferreira et al., 2009) (Fig. 1). These proteins regulate cell signalling by influencing mGlu1/5 receptor trafficking and surface expression (similarly to Homer), and also receptor dimerization, although they do not affect receptor coupling to signalling molecules. The mammalian homologue of Seven in Absentia (Siah-1A), a member of the RING-finger-containing E3 ubiquitin ligases, can also interact with the C-terminal domain of group-I mGlu receptors and this interaction promotes ubiquitination and degradation of group-I mGlu receptors (Moriyoshi et al., 2004). Binding of mGlu5 receptors with Siah-1A is competitively inhibited by calmodulin (Ishikawa et al., 1999), through a mechanism which involves a PKC-mediated phosphorylation of mGlu5 receptors (serine 901), and favours the internalization of mGlu5 receptors (Ko et al., 2012; Lee et al., 2008).

Regulation of group-I mGlu receptor signalling also involves mechanisms of receptor desensitization which are mediated by PKC and G-proteins-coupled receptor kinases (GRKs). PKC phosphorylates multiple sites in the second intracellular loop and C-terminus domains of mGlu1 and mGlu5 receptors, and mediates both homologous and heterologous desensitization of mGlu receptors (Catania et al., 1991; Gereau and Heinemann, 1998). NMDA receptor activation potentiates mGlu5 receptor function by reversing this mechanism of PKC-mediated receptor desensitization (Alagarsamy et al., 1999, 2005). Of note, a PKC-mediated phosphorylation of a particular threonine residue (T840) that is present in mGlu5 but not mGlu1 receptors, generates the oscillatory pattern of Ca^{2+} release from the intracellular stores (Kawabata et al., 1996), but has no impact on mGlu5 receptor desensitization. Phosphorylation by GRK2, GRK4, and GRK5, mediates homologous desensitization of mGlu1 receptors, whereas homologous desensitization of mGlu5 receptors is mediated by GRK2 and GRK3 (reviewed by Iacovelli et al., 2013).

2.3. Group-I mGlu receptors and mechanisms underlying activity dependent synaptic plasticity

Activation of mGlu5 receptors is involved in the induction of NMDA receptor-dependent Long Term Potentiation (LTP), induction of protein synthesis dependent LTD, and in mechanisms regulating depotentiation, *i.e.* the activity-dependent persistent reversal of previously established synaptic LTP.

Pivotal work in mice lacking mGlu5 receptors showed decreased NMDA-dependent LTP in the CA1 region and dentate gyrus (DG) of the hippocampus, and impaired hippocampal-dependent learning paradigms, such as learning acquisition in the water maze and contextual fear conditioning (Lu et al., 1997). The importance of mGlu5 receptors in potentiating NMDA currents and its role in facilitating NMDA receptor-dependent LTP has been confirmed in several studies (Attucci et al., 2001; Awad et al., 2000; Jia et al., 1998; Mannaioni et al., 2001; Pisani et al., 2001). mGlu5 receptor activation is also required for *in vivo* LTP and formation of working and reference memory, as shown by the use of the mGlu5 receptor negative allosteric modulator (NAM), 2-methyl-6-(phenylethynyl)pyridine (MPEP), in freely moving rats (Naie and Manahan-Vaughan, 2004). Potentiation of NMDA currents by mGlu5 receptor activation is mediated by the sequential activation of the focal adhesion kinase CAKb/Pyk2 and the tyrosine kinase, Src, with ensuing tyrosine phosphorylation of NMDA receptor subunits (Huang et al., 2001; Kotecha et al., 2003; Lu et al., 1999). Recent data suggest that a temporally coincident activation of group-I mGlu and NMDA receptors resulting into synaptic potentiation is critically dependent on the long Homer-mediated mGlu-NMDA receptor complex (Sylantyev et al., 2013).

While co-activation of mGlu5 and NMDA receptors induces LTP, activation of either mGlu1/5 or NMDA receptors alone induces LTD in the hippocampus (reviewed by Gladding et al., 2009). Group-I mGlu receptor-dependent LTD in particular, is altered in different mouse models of ID/autism. While a detailed discussion of mGlu-LTD mechanisms is beyond the scope of this review, there have been several excellent reviews focused on mGlu-LTD (Asrar and Jia, 2013; Gladding et al., 2009; Lüscher and Huber, 2010). It is believed that mGlu-LTD and NMDA-LTD use different induction

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mechanisms. mGlu-LTD is critically dependent on local protein synthesis in dendrites (Waung and Huber, 2009). Although protein synthesis is also involved in LTP and NMDA-LTD, in the particular case of mGlu-LTD new protein synthesis is required in a very short time window (within 5–10 min) (Huber et al., 2000). Expression of mGlu-LTD is ultimately caused by the endocytosis of AMPA receptors, which is triggered by several mechanisms also involving *de novo* synthesis of "LTD proteins", such as the striatal enriched tyrosine phosphatase (STEP) which dephosphorylates the AMPA receptor subunit, GluA2 (Moult et al., 2006; Zhang et al., 2008). Other candidate proteins are Arc/Arg3.1, which regulates AMPA receptor endocytosis by interacting with endophylin2/3 and dynamin (Chowdhury et al., 2006; Park et al., 2008; Waung et al., 2008), and microtubule-associated protein 1b (Map1b), which interacts with GRIP1 (Davidkova and Carroll, 2007).

The biochemical cascades linking group-I mGlu receptor activation to protein synthesis have been the object of intense investigation and have been extensively reviewed elsewhere (Bhakar et al., 2012; Waung and Huber, 2009). It is established that activation of group-I mGlu receptors leads to protein synthesis through ERK and mTOR signalling pathways; however the mechanisms which facilitate the translation of specific mRNAs are not clear. An interesting model recently proposed is that while activation of mTOR is required for increasing rate of overall mRNAs translation at synapse, ERK activation may control the translation of specific mRNAs, such as those encoding "LTD proteins" (Bhakar et al., 2012). In this context, the interaction of mGlu5 receptors with Homer may function as a molecular switch that regulates coupling to pathways regulating translation at different levels of initiation (mTOR and ERK) and elongation (eF2K) (Park et al., 2008; Ronesi et al., 2012).

In addition to a protein synthesis-dependent form of LTD, activation of group-I mGlu receptors triggers a form of LTD which is mediated by endocannabinoid formation and is independent of protein-synthesis (see below).

3. Dysregulation of mGlu5 receptor-mediated mechanisms in FXS

3.1. Local translation of synaptic mRNAs

FXS is the most common inherited form of ID and a leading genetic cause of autism (Abrahams and Geschwind, 2008; Kelleher and Bear, 2008). In addition to ID, FXS patients have a higher incidence of epilepsy and hypersensitivity to sensory stimuli, two features that are common in autism (Berg and Plioplys, 2012; Gilby and O'Brien, 2013). FXS is caused by the absence of the RNA binding protein fragile X mental retardation protein (FMRP), which regulates different aspects of RNA metabolism, including mRNA trafficking, stability and translational regulation (Maurin et al., this issue). No major brain malformation have been found in FXS; however, a higher density of dendritic spines, which appear long and immature, have been reported in both FXS patients and in the Fmr1 KO mouse model of the disease (Irwin et al., 2001; Nimchinsky et al., 2001). FXS was first linked to group-I mGlu receptors when FMRP was shown to be rapidly synthesized in synaptoneurosomes in response to group-I mGlu agonists (Weiler et al., 1997). This finding motivated subsequent studies that revealed enhanced group-I mGlu receptor-induced long-term synaptic LTD in hippocampal CA1 slices from Fmr1 KO mice (Huber et al., 2002). mGlu-LTD in wild type rodents requires rapid dendritic protein synthesis (see above) and mGlu-LTD in Fmr1 KO slices, in addition to being enhanced, is independent of new protein synthesis (Hou et al., 2006; Nosyreva and Huber, 2006). A major function of FMRP is to suppress translation of its target mRNAs. Recent work shows that FMRP suppresses the steady state translation of several proteins implicated in mGlu-LTD, and, upon group-I mGlu receptor activation, FMRP is dephosphorylated, ubiquitinated and degraded. This derepresses translation of its mRNA targets and contributes to rapid translational activation of proteins necessary for LTD such as Arc (Nalavadi et al., 2012; Niere et al., 2012). Therefore, in FXS there is an enhanced steady state level of proteins that promote LTD which likely underlies the LTD alterations associated with FXS.

It is important to note that FMRP directly interacts with >800 mRNAs, and 1/3 of these encode synaptic proteins (Darnell et al., 2011). As a consequence, there are many other synaptic phenotypes associated with FXS, some of which are likely independent of mGlu function (Pfeiffer and Huber, 2009 and Portera-Cailliau, 2012). However, the number and breadth of distinct phenotypes in FXS that are mediated by abnormal group-I mGlu receptor function are quite remarkable and illustrate that group-I mGlu receptor dysfunction is a large contributor to the pathophysiology of FXS (reviewed in Bhakar et al., 2012; Krueger and Bear, 2011). New data also demonstrate that group-I mGlu receptor dysfunction may also contribute generally to the pathophysiology of autism and related disorders.

3.2. mGlu5 receptor-dependent activation of endocannabinoid signalling

Endocannabinoids are ubiquitous modulators of cognitive functions and have received much attention as possible targets for diverse CNS diseases including psychiatric disorders (Campos et al., 2012). Several studies have recently addressed the question of whether endocannabinoid signalling activated by mGlu5 receptors might be altered in FXS. These reports show a dysregulation of the mGlu5 receptor-mediated endocannabinoid signalling; however, results are different depending on the brain area examined as well as on the endocannabinoid regulation of excitatory or inhibitory synaptic transmission, underscoring the complexity of the endocannabinoid system in the brain.

Activation of mGlu5 receptors increases levels of the endocannabinoid, 2-arachidonylglycerol (2-AG), *via* a sequential recruitment of PLC-β, which produce DAG, and DGLα, which converts DAG into 2-AG (Jung et al., 2005; Maccarrone et al., 2008; Varma et al., 2001). As mentioned before, coupling of mGlu5 receptors to DGLα is mediated by Homer proteins (Jung et al., 2007). 2-AG works as a retrograde messenger at several synapses and activates CB1 cannabinoid receptors on presynaptic terminals, thereby inhibiting neurotransmitter release at both excitatory and inhibitory synapses (depolarization-induced suppression of excitation and inhibition, respectively) (Chevaleyre et al., 2006). Evidence indicates that group-I mGlu receptor-induced, endocannabiniod-mediated regulation of both excitatory and inhibitory synapses is affected in FXS, but in opposite directions.

In medium spiny neurons of the ventral striatum and pyramidal neurons of the prefrontal cortex mGlu5 receptor-dependent formation of 2-AG is responsible for a form of LTD which is independent of protein synthesis (Lafourcade et al., 2007; Robbe et al., 2002). Jung and collaborators (2012) reported a marked deficit of this mGlu5-mediated 2-AG dependent form of LTD in both ventral striatum and prefrontal cortex of Fmr1 KO mice, which was normalized by pharmacological enhancement of 2-AG signalling. These authors propose that impairment of this form of LTD in FXS is caused by the uncoupling of 2-AG formation from mGlu5 receptors, which is likely due to a physical disruption of the multiprotein complex linking mGlu5 receptors to DGL-α at the perisynaptic annulus of dendritic spines. They found that in the brain of Fmr1 KO mice DGL-α is concentrated at the neck of dendritic spines rather than being localized close to the membrane in the perisynaptic region. This intracellular retention might be caused by an altered targeting

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of the mRNA encoding DGL-α, which is linked to FMRP, and may be incorrectly translated. Alternatively, or in addition, disruption of long Homer-DGL-α binding may cause intracellular retention of the enzyme (Jung et al., 2007) and deficits in mGlu-activated retrograde 2-AG signalling at excitatory synapses (Roloff et al., 2010). The mGlu5 receptor is known to be uncoupled from the long Homer scaffolding proteins in FXS (Giuffrida et al., 2005; Ronesi et al., 2012). An interesting possibility is that Homer scaffolds to other proteins are also disrupted in FXS which affects the function and localization of multiple Homer binding proteins, such as DGL-α.

In the hippocampus, activation of mGlu5 receptors on pyramidal cells of the CA1 region triggers the formation of endocannabinoids, which inhibit GABA release by acting retrogradely on CB1 receptors. CB1 receptors are abundantly expressed on pre-synaptic terminals of GABAergic/Cholecystokinin positive interneurons (Katona et al., 1999; Wilson and Nicoll, 2001). An enhanced mGlu5/endocannabinoid-mediated responses at GABAergic synapses has been detected in the CA1 region of Fmr1 KO mice (Zhang and Alger, 2010). Similar findings have been reported in striatal neurons, where the mGlu5/endocannabinoid-dependent inhibition of mIPSC frequency is markedly enhanced in Fmr1 KO mice (Maccarrone et al., 2010). Interestingly both MPEP binding and DGL activity are also enhanced in the striatum of Fmr1 KO mice (Maccarrone et al., 2010). Another possibility is that the opposite phenotypes of endocannabinoid regulation at inhibitory and excitatory synapses in FXS may be explained by the mis- or re-localization of DGL-α within spines. Indeed, many inhibitory synapses occur adjacent to spine necks and GABAergic presynaptic terminals are thought to receive 2-AG synthesized from DGL-α at spine necks. In contrast, DGL-α localized near the spine head is expected to concentrate 2-AG near excitatory pre-synaptic terminals (Yoshida et al., 2006). The redistribution of DGL-α away from the spine head to the spine neck in FXS may redistribute 2-AG away from excitatory synapses and towards inhibitory synapses; this leads to the distinct phenotypes that depend on the type of synapse.

In line with a potential involvement of the endocannabinoid signalling in the pathophysiology of FXS, translational studies showed that both acute and chronic administration of the CB1 receptor antagonist, rimonabant, reverted the deficit of object recognition memory consolidation test, similarly to chronic treatments with the mGlu5 receptor NAM MTEP and the mTOR inhibitor, sirolimus. Interestingly, rimonabant and MPEP produced additive effects in correcting the increased phosphorylation of p70S6K (Thr381) and Akt (Ser473) and the altered spine morphology in FXS mice, suggesting in this case an independence of the mGlu5 and the endocannabinoid pathways (Busquets-Garcia et al., 2013). These data are not consistent with the evidence that 2-AG boosting with an inhibitor of monoacylglycerol lipase in Fmr1 KO mice corrects the increased locomotor activity in the open field and anxiety-like behaviour in the elevated plus maze (Jung et al., 2012). Because endocannabinoid regulation of distinct synapse types is differentially affected in FXS, it is unlikely that general inhibition or activation of the endocannabinoid system will rescue all phenotypes. Therefore, development of therapeutics to target endocannabinoid function selectively at excitatory or inhibitory synapses could be useful for treating FXS.

3.3. *mGlu5 signalling pathways underlying neuronal network excitability and cortical oscillations*

Alterations in cortical network activity may underlie both cognitive and behavioural dysfunctions in FXS and other disorders characterized by ID and autism. Furthermore, an imbalance between local recurrent excitation and inhibition might be the basis for the sensory hypersensitivity and increased susceptibility of epileptic seizures associated with FXS and other developmental disorders. Enhanced mGlu5 receptor function is implicated in audiogenic seizures and specific hyperexcitability of specific circuits in the sensory neocortex and hippocampal CA3 neurons in Fmr1 KO mice.

One of the most robust phenotypes in the Fmr1 KO mice is audiogenic seizures, or seizures in response to a loud noise (Musumeci et al., 2007, 2000). Pharmacological antagonism of mGlu5 completely blocks audiogenic seizures in Fmr1 KO mice (Yan et al., 2005). Similarly, genetic reduction of mGlu5, by crossing mice that are heterozygous for mGlu receptor 5 (Grm5+/−) with Fmr1 KO mice reduces the incidence and severity of audiogenic seizures (Dolen and Bear, 2008). One of the first evidence for mGlu-mediated hyperexcitability of specific circuits is the work of Wong and colleagues showing that blockade of GABAergic inhibition in area CA3 of Fmr1 KO hippocampal slices leads to prolonged epileptiform bursts of action potentials in comparison to the short bursts observed in slices from wild type mice. These prolonged bursts are blocked by the mGlu5 receptor antagonist, MPEP, as well as by inhibitors of protein synthesis or the ERK pathway (Bianchi et al., 2009; Chuang et al., 2005). Strong activation of mGlu5 receptors with an agonist is required in wild type animals to generate the bursts. Therefore, weaker synaptic activation of mGlu5 is sufficient to trigger the epileptiform bursts and translation of proteins that lead to the prolonged epileptiform bursts (Chuang et al., 2005). Similar mechanisms may underlie audiogenic seizures in Fmr1 KO mice because inhibitors of the ERK pathway, applied acutely *in vivo*, also block seizures (Osterweil et al., 2013, 2010).

Studies in slices and *in vivo* somatosensory, barrel cortex have identified alterations in spontaneous oscillations of circuit activity that reflect hyperexcitable circuits. Persistent activity states, or UP states, were found to be longer in duration in neocortical slices obtained from Fmr1 KO mice. UP states are depolarized firing states of neurons that are driven by recurrent excitation and occur synchronously among all neurons in a cortical region (Haider and McCormick, 2009; Sanchez-Vives et al., 2010). When UP states occur spontaneously and repeatedly, they underlie the neocortical "slow oscillation" (<1 Hz) during slow wave sleep and may be involved in long-term memory consolidation (Crunelli and Hughes, 2010; Ji and Wilson, 2007; Marshall and Born, 2007; Marshall et al., 2006). Therefore, altered UP states may modify the slow oscillation in FXS which, in turn, may lead to impaired cognition. Prolonged UP states are caused by deletion of Fmr1 in excitatory neurons and are mediated by enhanced mGlu5 receptor signalling. Genetic reduction and pharmacological blockade of mGlu5, but not mGlu1, receptors rescue the prolonged UP states as measured in acute slices of neocortex or *in vivo* of anesthetized Fmr1 KO mice (Hays et al., 2011). Importantly, this mGlu5-dependent phenotype of Fmr1 KO mice does not depend on rapid mRNA translation (Hays et al., 2011), but does depend on ERK activation (Collins, Gibson and Huber, unpublished) implicating an mGlu5 and ERK-dependent post-translational mechanism in circuit hyperexcitability. Recent work indicates that a disruption of the mGlu5-Homer interactions leads to circuit hyperexcitability and seizures. Peptide-mediated disruption leads to prolonged UP states in wild type neocortical slices, and restoration of mGlu5-long Homer scaffolds in Fmr1 KO mice, by deleting Homer1a, shortens UP states to wild type levels and reduces the incidence of audiogenic seizures (Ronesi et al., 2012). These results suggest that mGlu5 receptors, when disrupted from Homer scaffolds lead to enhanced mGlu5-driven ERK activity, which causes circuit hyperexcitability. Identification of the channels and/or synaptic mechanisms that are regulated by mGlu5 and ERK is an important goal to understand and treat the etiology of circuit dysfunction in FXS.

Please cite this article in press as: D'Antoni, S., et al., Dysregulation of group-I metabotropic glutamate (mGlu) receptor mediated signalling in disorders associated with Intellectual Disability and Autism. Neurosci. Biobehav. Rev. (2014), http://dx.doi.org/10.1016/j.neubiorev.2014.02.003

mGlu5-Homer uncoupling and ID/autism related disorders

The core of pathophysiological mechanisms underlying FXS and ID/autism-related disorders has been related to dysfunctional protein synthesis at synapses. Recent evidence suggests however that some relevant phenotypes might depend also on other mechanisms. Here, we highlight findings which suggest that mGlu5-Homer uncoupling may be a mechanism underlying the physiopathology of ID- and autism-related disorders.

mGlu5 receptors are less associated with constitutive long Homer in synaptosomal preparations from forebrain of Fmr1 KO mice, suggesting alterations in mGlu5 receptor trafficking, localization and function (Giuffrida et al., 2005). Disruption of mGlu5-Homer interaction by a cell-permeable Tat-peptide containing the proline-rich motif of the mGlu5 receptor C-terminal inhibits group-I mGlu receptor activation of the PI3K-mTOR pathway, but does not affect ERK pathway, and inhibits mGlu-LTD (Ronesi and Huber, 2008). In Fmr1 KO mice, activation of group-I mGlu receptors fails to activate mTOR pathway and induces LTD independently of Homer interaction (Ronesi and Huber, 2008). Interestingly, mGlu5-Homer interaction exerts an inhibitory control on eEF2K, which in turn phosphorylates eEF2, thus slowing the elongation step of translation and inhibiting general protein synthesis. This step is believed to favour the rapid synthesis of specific proteins, *i.e.* Arc (Park et al., 2008).

Deletion of Homer1a, which shifts the equilibrium towards mGlu5-Homer association, restored increased rate of total protein synthesis in Fmr1 KO mice to wild type levels, but did not correct increased mGlu-dependent LTD nor increased levels of "LTD proteins" (Ronesi et al., 2012). Thus, disruption of mGlu5-Homer interaction is not involved in the abnormal translational control of FMRP target mRNAs. In contrast, Homer1a deletion corrected prolonged UP states and open field activity phenotypes and reduced susceptibility to audiogenic seizures in Fmr1 KO mice (Ronesi et al., 2012).

Increased cortical excitability, seizures and anxiety are frequent in autism related disorders. While increased mGlu-LTD is a "specific" phenotype of FXS, disruption of mGlu5-Homer may underlie symptoms which are in common with other disorders. Recent data which identified rare and potentially deleterious Homer1 single-nucleotide variants (SNV) in a population of non syndromic autism are in line with this view (Kelleher et al., 2012; see Section 5 for details).

4. mGlu5 signalling to translation and plasticity are altered in different models of ID/autism

Pivotal work in the FXS mouse model highlighted changes in protein synthesis-dependent and protein synthesis-independent synaptic plasticity mediated by mGlu5 receptors, as described above. This work has been extended recently to other mouse models of both ID and autism and suggests that mGlu5-dependent plastic changes may also be central in the pathophysiology of these disorders. These results are summarized in Table 1.

4.1. Tuberous sclerosis complex (TSC)

TSC is a multi-systemic disease characterized by predisposition to tumour formation in several organs and developmental problems. The occurrence of cortical tubers and subependymal nodules in the brain is associated with seizures and cognitive impairment. Autism is also prevalent in TSC being present in 25–50% of patients (Wiznitzer, 2004). TSC is an autosomal dominant disorder caused by mutations in the genes TSC1 and TSC2, encoding the tumour suppressor proteins, hamartin (TSC1) and tuberin (TSC2). These two proteins behave as GAPs (GTPase-activating proteins) of the small GTP-binding protein, Rheb (Ras homologue enriched in brain), thereby restraining the activation of mTORC1 (mammalian target of rapamycin complex 1) (Huang and Manning, 2008). Hence, a defective activity of hamartin and tuberin causes hyperactivity of mTORC1 with resulting enhancement of phosphorylation of p70S6K, mRNA translation, and cell growth. Work in mouse models of TSC indicates that cognitive dysfunction may occur in the absence of brain lesions and epilepsy (Goorden et al., 2007). By analogy with Fmr1 KO mice, it was initially hypothesized that an increased mGlu5 receptor-dependent LTD could also be associated with TSC. In contrast, mGlu5 receptor-dependent LTD was rather abolished in the CA1 region following acute post-synaptic loss of TSC1 (Bateup et al., 2011). A similar reduction of mGlu5 receptor-dependent LTD was found in a mouse model of TSC carrying a heterozygous loss of mutation in Tsc2 in the absence of changes in basal synaptic transmission and NMDA receptor-dependent-LTD (Auerbach et al., 2011). mGlu5 receptor-dependent LTD (but not NMDA receptor-dependent LTD) was also impaired in a different mouse model of TSC, carrying a deletion of amino acid residues 1617–1655 and a substitution of amino acid residues 1679–1742 (ΔRG transgenic mouse), which interfere with the ability of TCS2 to hydrolyse GTP-bound to Rap1 and Rheb (Chévere-Torres et al., 2012). Thus, a reduction of mGlu5 receptor-dependent LTD has been consistently found in different mouse models of TSC. The biochemical mechanisms underlying these effects are unclear. While a constitutive up-regulation of mTOR signalling, which is indicative of an increased protein synthesis, was found in a conditional Tsc1 KO mouse (Bateup et al., 2011), a reduction of ^{35}S-methionine incorporation and newly synthesized Arc protein was detected in the hippocampus of Tsc2$^{-/+}$ mice (Auerbach et al., 2011). This apparent discrepancy was explained by the suppressive activity exerted by mTORC-dependent proteins over the synthesis of a set of other proteins that are regulated by mGlu5 receptors and sustain LTD (Auerbach et al., 2011). Accordingly, rapamycin restored mGlu5 receptor-dependent LTD, but its effect was abolished by the protein synthesis inhibitor cycloheximide (Auerbach et al., 2011). Thus, the biochemical mechanism underlying reduced mGlu-LTD in Tsc2$^{-/+}$ mice involves a reduction of synthesis of "LTD proteins", which is opposite to that responsible for increased mGlu5 receptor-dependent LTD in Fmr1 KO mice. Interestingly, the mGlu5 receptor positive allosteric modulator (PAM), 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)-benzamide (CDPPB), restored mGlu5 receptor-dependent-LTD in Tsc2$^{-/+}$ mice and mice carrying both Fmr1 and Tsc2 deletion showed normal mGlu5 receptor-dependent LTD (Auerbach et al., 2011). This finding has important implications for the pathophysiology of ID associated with autism because deviation in opposite direction in similar biochemical mechanisms might underlie common pathological phenotypes. In addition, the appropriate treatment for a specific autism-spectrum disorder may be detrimental for another disorder.

4.2. Macrocephaly/autism syndrome

The tumour-suppressor gene, phosphatase and tensin homolog (PTEN) is a well established candidate gene in autism. PTEN germline loss of function mutations have been found in a subset of children affected by macrocephaly, autism spectrum disorders and ID, and PTEN mutation are present in about 5–10% of autistic patients (McBride et al., 2010; Zhou and Parada, 2012). PTEN is an established tumour suppressor gene that is mutated in several types of cancers, and encodes for a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase which behaves as an inhibitor of the PI3K/mTOR/AKT pathway. A conditional KO mouse in which Pten is selectively ablated in granule cells of the dentate gyrus, and in pyramidal neurons of the CA3 region shows features resembling the human condition, such as abnormal social interaction

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Table 1
Summary of evidence suggesting involvement of group-I mGlu receptors in syndromic and non syndromic form of ID/autism.

DiseasE	Gene	OMIM number	Model	mGlu1/5-LTD	Signalling pathways to protein synthesis	mGlu1/5 receptors proteins expression	References
Fragile X syndrome	*FMR1*	#300624	Fmr1 KO mouse	↑ mGlu5-LTD (hippocampus),[1] ↑ mGlu1-LTD (cerebellum),[2] ↓ mGlu5-LTD (eCB dependent, ventral striatum and prefrontal cortex),[3] ↑ mGlu5-LTD (eCB dependent, striatum)[4]	↑ mTOR (basal),[5–7] ↓ mTOR DHPG induced,[8] - ERK (basal and DHPG induced)[9]	↑ mGlu5[4,10,11]	[1]Huber et al., 2002; [2]Koekkoek et al., 2005; [3]Jung et al., 2012; [4]Maccarrone et al., 2010; [5]Gross et al., 2010; [6]Sharma et al., 2010; [7]Busquets-Garcia et al., 2013; [8]Ronesi and Huber, 2008; [9]Osterweil et al., 2010; [10]Lohith et al., 2013; [11]Spatuzza et al., unpublished
Tuberous sclerosis complex	*TSC1*	#191100	Tsc1 conditional KO mouse (deletion of Tsc1 in a subset of hippocampal CA1 neurons)	↓ mGlu5-LTD (hippocampus)	↑ mTOR (basal)[1]	↑ mGlu1[2] ↑ mGlu5[2]	[1]Bateup et al., 2011; [2]Boer et al., 2008
	TSC2	#613254	ΔRG transgenic mouse carrying a deletion and a substitution in Tsc2 which interferes with both the GAP domain and rabaptin-5 binding motif	↓ mGlu5-LTD (hippocampus)	↑ ERK (basal) - mTOR	N.D.	Chévere-Torres et al., 2012
			Tsc2 +/− mouse	↓ mGlu5-LTD (hippocampus)	- ERK (basal and DHPG induced)	N.D.	Auerbach et al., 2012
Macrocephaly/autism syndrome	*PTEN*	#605309	Pten conditional KO mouse (ablation of Pten in the granule cells of the dentate gyrus, pyramidal neurons of the hippocampal CA3 and select populations of postmitotic neurons in the cortex	↓ mGlu5-LTD (hippocampus)[1]	↑ mTOR (basal)[2]	N.D.	[1]Takeuchi et al., 2013; [2]Kwon et al., 2006
Phelan McDermid syndrome	*SHANK 3*	#606232	Shank knockdown (cultured hippocampal neurons)	↓ mGlu5-LTD	↓ ERK (DHPG induced)	↓ mGlu5	Verpelli et al., 2011
Obsessive–compulsive disorder	*SAPAP 3*	#164230	Sapap3 KO mouse	↑ mGlu5-LTD (eCB dependent, striatum)[1]	N.D.	↑ mGlu5 (striatum)[2]	[1]Chen et al., 2011; [2]Wan et al., 2011
Non-syndromic form of autism	*NLGN3*	*300336	Nlgn3 KO mouse	absent mGlu1-LTD (cerebellum)	N.D.	↑ mGlu1 (cerebellum and thalamus)	Baudoin et al., 2012

↑ increased; ↓ reduced; - unchanged.
eCB: endocannabinoid; DHPG: (RS)-3,5-dihydroxyphenylglycine; LTD: long term depression; N.D.: not determined.

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and exaggerated responses to sensory stimuli, as well as macrocephaly and neuronal hypertrophy (Kwon et al., 2006). A reduction of group-I mGlu receptor-dependent LTD and an increased theta burst-induced LTP were detected at the perforant path/dentate gyrus granule cells synapses before the onset of morphological defects in Pten-deficient mice. These forms of synaptic plasticity are PI3 kinase- and protein synthesis-dependent, and their early dysregulation supports the hypothesis of a synaptic defect in autism. Interestingly, while the increased LTP is transient during development, the defect in mGlu5 receptor-dependent LTD is permanent in these mice, indicating a requirement of PTEN for these forms of plasticity, at least at these synapses (Takeuchi et al., 2013).

4.3. Phelan McDermid/22q13 deletion

Accumulating evidence suggests that molecular defects of SHANK proteins are associated with autism (Jiang and Ehlers, 2013). SHANK/ProSAP proteins (SHANK1, 2 and 3) are postsynaptic scaffolding proteins that regulate the size of dendritic spines and the recruitment of post-synaptic receptor complexes. Importantly, SHANK proteins function as a molecular link between mGlu1/5 receptors and NMDA receptors through a chain of interacting proteins including mGlu1/5 receptors, long Homers, Shank, GKAP, and GluN2 subunits of NMDA receptors (Fig. 1). Mutations of SHANK3/PROSAP2 gene are cause of 22q13 deletion/Phelan Mc Dermid syndrome, a neurodevelopmental disorder characterized by developmental delay, hypotonia, language impairment, mild ID and autistic features (Phelan, 2008). Furthermore, mutations of SHANK3 are the most frequent among the rare variants found in autism (for review see Betancur and Buxbaum, 2013; Bourgeron, 2009) and have also been detected in non syndromic form of ID (Gong et al., 2012). More recently, SHANK1 and SHANK2 have been also implicated in autism (Berkel et al., 2010; Sato et al., 2012). Several mutant mice for all Shank family genes have been created and all of them exhibit abnormalities in social behaviour resembling autistic features (Jiang and Ehlers, 2013; Wang et al., 2014). Glutamatergic transmission and synaptic plasticity is variously impaired in most of these models although a specific involvement of mGlu receptor mediated transmission has not been identified. However, in Shank 1 and Shank 3 mutant mice a reduction of Homer1 proteins might implicate an alteration of mGlu5-mediated signalling in these mutant mice (Hung et al., 2008; Peça et al., 2011; Wang et al., 2011), whereas only NMDA receptor mediated signalling appear to be impaired in Shank 2 mutant mice (Won et al., 2012). In contrast with evidence from Shank mutant mice in which single splice variants are affected, a recent *in vitro* study, in which the expression of all the major Shank3 splice variants have been knocked down through RNA interference, suggests that dysfunctional mGlu5 receptor signalling might be involved in the pathophysiology of 22q13 deletion/Phelan Mc Dermid syndrome (Verpelli et al., 2011). They found that knockdown of Shank3 causes a specific reduction in the expression of mGlu5 receptors, whereas levels of NMDA and AMPA receptor subunits, Homer and GKAP were unchanged. The lower mGlu5 receptor expression was associated with a reduced DHPG-stimulated ERK1/2 and CREB phosphorylation and mGlu5 receptor-dependent decrease of mEPSC frequency, a form of mGlu5 receptor-dependent LTD in cultured neurons. Interestingly, defects in mGlu5 receptor-dependent ERK1/2 phosphorylation were not rescued by overexpression of two Shank3 carrying mutations that have been found in patients with autism (Durand et al., 2007), suggesting that alteration of mGlu5 receptor signalling might be a common mechanism in Phelan Mc Dermid disease and non syndromic form of autism linked to Shank3 mutations. The observed reduction of mGlu5 receptor-dependent ERK1/2 phosphorylation in Shank3-deficient neurons was corrected by enhancement of mGlu5 receptor activity induced by the selective PAM, CDPPB. While in disorders associated to SHANK3 mutation mGlu5 PAMs might work by restoring the function of mGlu5 receptors, they may also be beneficial in other forms of ASD, such as those caused by mutations of SHANK2 where they promote the mGlu5-mediated enhancement of NMDA function (Won et al., 2012).

4.4. Obsessive compulsive disorder (OCD)

Another interesting example of mutations of scaffolding proteins affecting mGlu5 signalling and possible involvement of dysfunctional mGlu5 mediated transmission in autism related disorders is the Sapap3 KO model of obsessive-compulsive disorder (OCD). Symptoms of OCD are thought to be related to the repetitive behaviours which are a hallmark of autism. SAP90/PSD-95 associated proteins (SAPAPs, also referred to as GKAPs) are scaffolding proteins linking NMDA/PSD95 complex to mGlu/Homer (Kim et al., 1997; Takeuchi et al., 1997; Tu et al., 1999). SAPAP3 is one of four isoforms and is highly expressed in the striatum. Mice carrying a deletion of Sapap3 gene exhibit features resembling obsessive compulsive behaviour such as excessive grooming, excessive anxiety, facial lesions and positive response to fluoxetine (Welch et al., 2007). In this mouse model, an excessive endocannabinoid mediated depression was detected at excitatory synapses of striatal medium spiny neurons which was caused by increased mGlu5 receptor expression/activity (Chen et al., 2011). MPEP was shown to correct the excessive eCB-mediated plasticity and both an increased surface expression of mGlu5 receptors and an increased intracellular calcium release in response to the mGlu1/5 receptor orthosteric agonist DHPG was detected in Sapap3 mice. Thus, SAPAP3 like Homer proteins can regulate the expression of mGlu5 receptors. Intriguingly this phenotype is similar to that described in the striatum of FXS mouse model by Maccarrone et al. (2010) and may underlie compulsive-repetitive behaviour in different disorders. The increased mGlu5 receptor activity is also responsible for an increased AMPA receptor endocytosis that is independent on endocannabinoids (Wan et al., 2011), pointing again to commonality with mGlu5-dependent AMPA receptor endocytosis observed in FXS (Nakamoto et al., 2007). It would be interesting to know whether this effect is caused by an increased mGlu5-mediated striatal protein synthesis. Furthermore, the mechanisms which lead to the increased expression of mGlu5 receptors in the absence of SAPAP3 are unknown.

4.5. Non-syndromic autism

A further evidence that group-I mGlu receptors may be involved in non-syndromic form of autism is provided by a recent study carried out on the neuroligin-3 (Nlgn3) KO mouse model of autism (Baudouin et al., 2012). NLGN genes encode post-synaptic adhesion molecules (neuroligin 1–4) involved in post-synaptic assembly and regulation of synaptic transmission *via* interaction with presynaptic neurexins (Craig and Kang, 2007). Mutations in both neuroligin and neurexin genes have been found to be associated with non-syndromic forms of autism; for Nlgn3, a R451C point mutation and deletion have been identified in several patients with autism, and a Nlgn3 KO and Nlgn R451C knockin mice exhibit features of autistic behaviour. Nlgn3 KO mice exhibit a striking increase in the expression of mGlu1 receptors in the cerebellum which is associated with an occlusion of group-I mGlu receptor induced LTD at parallel fibres–Purkinje cell synapses (Baudouin et al., 2012).

Other work implicates enhanced mGlu5 receptor function in autistic like behaviours in mice. The BTBR mouse is an inbred mouse strain that shows robust behaviours analogous to autism in humans, such as reduced social interaction, repetitive behaviours

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and altered vocalizations (McFarlane et al., 2008). Recent studies demonstrated that mGlu5 receptor antagonists reversed the repetitive behaviours and enhanced social interactions in the BTBR mice (Silverman et al., 2012, 2010) suggesting that dysfunction of mGlu5 receptors leads to behaviours with face validity for autism.

5. Group-I mGlu receptor expression/signalling may be a common feature of syndromic and non syndromic autism

The first studies aimed at investigating the expression of mGlu5 receptor in the brain of Fragile X mouse models revealed no changes in levels of protein expression in hippocampal homogenates (Huber et al., 2002) and forebrain synaptosomes (Giuffrida et al., 2005). More recent evidence, however, suggests that changes in the expression of mGlu5 receptors may be associated with FXS. Accordingly, an increased MPEP binding has been found in the striatum of Fmr1 KO mice (Maccarrone et al., 2010). We have also found that mGlu5 expression is up-regulated in a region- and age-specific manner in a mouse model of FXS (Spatuzza, D'Antoni, Catania, unpublished). The possibility that mGlu5 receptors might be up-regulated is further strengthened by the evidence that mGlu5 mRNA directly interacts with FMRP (Darnell et al., 2011). Interestingly, a striking up-regulation of mGlu5 receptors in children with autism has been associated with a reduction of FMRP, further corroborating the idea that FMRP might be a key regulator of mGlu5 expression (Fatemi et al., 2011). A recent study, using *in-vitro* radioligand binding assays and Western blotting reports a marginally significant increase in mGlu5 receptor density (+16%) and a statistically significant increase in mGlu5 receptor expression in the postmortem prefrontal cortex of FXS patients or carriers, compared with age- and sex-matched controls without neurological disorders (Lohith et al., 2013).

An increased expression of mGlu1/mGlu5 receptors has been detected in human specimens from TSC, namely in dysplastic neurons and in giant cells within cortical tubers, as well as in tumour cells within subependymal giant-cell tumours (Boer et al., 2008).

An involvement of group-I mGlu receptor signalling in autism is also suggested by a recent work which identified rare and potentially deleterious Homer1 single-nucleotide variants (SNV) exclusively in a population of non syndromic autism cases compared to ethnically-matched controls, by high-throughput multiplex sequencing (Kelleher et al., 2012). Interestingly, all of the identified missense mutations alter residues which are conserved among mammalian species; two of these SNV localize to the EVH domain of Homer1, one is located in a proline rich domain which is also important for interaction with mGlu receptor or Homer1 homo-multimerization, and a fourth one is located in the 3′ untranslated region within a cluster of predicted microRNA binding sites, with possible consequences in HOMER1 mRNA translation and protein expression (Kelleher et al., 2012).

6. Conclusion

Several lines of evidence point to a major involvement of mGlu receptor signalling as a common pathway in several disorders associated to ID and autism. mGlu-receptor mediated plasticity, namely mGlu-LTD, has been studied as an important read-out of mGlu receptor activation in different brain regions in several ID/autism mouse models and found either increased or decreased. Work in FXS shows that while some phenotypes are critically dependent on mGlu-activated protein synthesis others implicate additional mechanisms such as endocannabinoid signalling and mGlu1/5-Homer coupling. Finally, an increased expression of mGlu1/5 receptor protein has been detected both in human specimens and mouse models. Although more studies are necessary to dissect the molecular mechanisms which lead to changes in mGlu1 and 5 receptor expression in autism, these studies suggest that group-I mGlu receptors may be key regulators of autistic endophenotypes in syndromic forms of autism and may be targeted by therapeutic intervention in non syndromic forms of autism.

Acknowledgements

The authors thank FRAXA Research Foundation, Telethon Onlus Foundation (projects GGP07264 and GGP13145) and IRCCS Oasi Maria SS. (Troina) for support.

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Please cite this article in press as: D'Antoni, S., et al., Dysregulation of group-I metabotropic glutamate (mGlu) receptor mediated signalling in disorders associated with Intellectual Disability and Autism. Neurosci. Biobehav. Rev. (2014), http://dx.doi.org/10.1016/j.neubiorev.2014.02.003

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Please cite this article in press as: D'Antoni, S., et al., Dysregulation of group-I metabotropic glutamate (mGlu) receptor mediated signalling in disorders associated with Intellectual Disability and Autism. Neurosci. Biobehav. Rev. (2014), http://dx.doi.org/10.1016/j.neubiorev.2014.02.003

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