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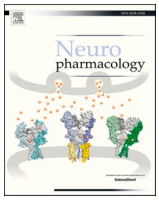

Metabotropic actions of kainate receptors modulating glutamate release

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A B S T R A C T

Presynaptic kainate (KA) receptors (KARs) modulate GABA and glutamate release in the central nervous system of mammals. While some of the actions of KARs are ionotropic, metabotropic actions for these receptors have also been seen to modulate both GABA and glutamate release. In general, presynaptic KARs modulate glutamate release through their metabotropic actions in a biphasic manner, with low KA concentrations producing an increase in glutamate release and higher concentrations of KA driving weaker release of this neurotransmitter. Different molecular mechanisms are involved in this modulation of glutamate release, with a G-protein independent, Ca^{2+}-calmodulin adenylate cyclase (AC) and protein kinase A (PKA) dependent mechanism facilitating glutamate release, and a G-protein, AC and PKA dependent mechanism mediating the decrease in neurotransmitter release. Here, we describe the events underlying the KAR modulation of glutamatergic transmission in different brain regions, addressing the possible functions of this modulation and proposing future research lines in this field.

1. Introduction

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system (CNS) of mammals, its actions mediated by the activation of glutamate receptors. These receptors participate in normal synaptic transmission, plasticity, synaptogenesis and neuronal maturation, and errant functioning of this system may provoke some types of epilepsy or contribute to other different CNS disorders (Traynelis et al., 2010; Flores et al., 2012). Glutamate receptors are classically divided into two large families: ionotropic and metabotropic. The ionotropic glutamate receptors (iGluRs) participate in rapid neurotransmission and they are classified into three types depending on the agonist that activates them with highest affinity: N-methyl-D-aspartic acid (NMDA) receptors (NMDARs); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs); and kainate (KA) receptors (KARs). These receptors form a channel with different selectivity depending on their subunit composition, all of them are permeable to Na^+ and K^+. Moreover, NMDARs are permeable to Ca^{2+}, with some AMPARs and KARs also displaying Ca^{2+} permeability depending on their subunit composition (Traynelis et al., 2010). Metabotropic glutamate receptors (mGluRs) participate in "slow" neurotransmission, they are coupled to G-proteins, and they are divided into eight types (mGluR 1–8) and three groups: group I that includes mGluR1 and mGluR5 receptors positively coupled to phospholipase C (PLC); Group II that includes mGluR2 and mGluR3 receptors; and group III that includes mGluR4, mGluR6, mGluR7 and mGluR8 receptors, all negatively coupled to adenylate cyclase-mediated cAMP formation (Niswender and Conn, 2010).

The distinction between "ionotropic" and "metabotropic" receptors seems to be more complex than anticipated, and the three glutamate receptors typically considered to be ionotropic (NMDARs, AMPARs and KARs) have also been defined as having additional non-ionotropic or direct metabotropic actions. AMPARs are well known mediators of the majority of fast excitatory neurotransmission in the CNS, yet some of their actions are sensitive to G proteins. For instance, they activate MAPK kinases in a pertussis toxin (PTX) sensitive manner, suggesting the involvement of a G protein (Wang and Durkin, 1995), and they interact with G_i proteins (Wang et al., 1997). Synaptically, AMPARs with a metabotropic role in the cerebellum have been found to participate in the control of GABA release onto Purkinje cells (Satake et al., 2004). NMDARs with a metabotropic action have been proposed to participate in long-term depression (LTD) in the hippocampus (Nabavi et al., 2013, but see Babiec et al., 2014) and cerebellum (Kakegawa et al., 2007), and recently, a metabotropic role for presynaptic NMDARs was defined in the visual cortex, controlling spontaneous (but not evoked) glutamate release (Abrahamsson et al., 2017; Bouvier et al., 2018).

The first glutamate receptors typically considered ionotropic to be

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attributed a physiological metabotropic activity were the KARs in the hippocampus (Rodríguez-Moreno and Lerma, 1998). KARs are typically tetramers made up of different combinations of GluK1-GluK5 subunits encoded by the *Grik* 1–5 genes. GluK1-GluK3 may form homomeric or heteromeric receptors, while GluK4 and GluK5 may only participate in functional receptors when associated with any of the GluK1-GluK3 subunits. KARs have been described in different invertebrates like nematodes and flies (Lee, 2002), and in different vertebrates including amphibians, fish, birds (Li et al., 2016; Somogyi et al., 1990; Atoji and Sarkar, 2019; Estabel et al., 1999) and mammals. In mammals, KARs have been found in virtually the entire nervous system, although their subcellular location has yet to be fully defined (Paternain et al., 2000; Huettner, 2003; Jane et al., 2009). Genetic deficits in *Grik* 1–5 genes or incorrect KAR activity are involved in some brain alterations and diseases, including epilepsy, ischemia, stress and anxiety, Autism Spectrum Disorders (ASDs), Schizophrenia, bipolar disorder and mental retardation (reviewed in Lerma and Marques, 2013). As these receptors have different intracellular effects, to fully understand the activities of KARs, and to prevent/treat these brain alterations and diseases, it is fundamental to define both their ionotropic and metabotropic mechanisms, as well as the intracellular cascades involved in KAR activities. Since the discovery of the metabotropic functions of KARs in the hippocampus in 1998, metabotropic activities of KARs in modulating neurotransmitter release have been found at a number of synapses, participating in synaptic plasticity and modulating cell excitability (reviewed in Rodríguez-Moreno and Sihra, 2007a, b, 2011a,b; Sihra and Rodríguez-Moreno, 2011, 2013, Sihra et al., 2014; Valbuena and Lerma, 2016; Negrete-Díaz et al., 2018).

At synapses, KARs are known to mediate synaptic transmission postsynaptically and modulate neurotransmitter release at different synapses presynaptically. Postsynaptically, KARs participate in synaptic transmission by mediating a small current with slow activation and deactivation kinetics in some synapses, e.g. mossy fiber (MF)-CA3 synapses (Castillo et al., 1997; Vignes and Collingridge, 1997; Cossart et al., 1998; Frerking et al., 1998; Li and Rogawski, 1998; Li et al., 1999; Kidd and Isaac, 1999; Bureau et al., 2000). In the hippocampus, KARs participate in the control of neuronal excitability by inhibiting the afterhyperpolarization currents (I_{AHP}) when activated by KA or glutamate, causing a clear increase in action potential firing frequency of CA1 pyramidal cells (PCs). Interestingly, this activity requires KARs coupled to $G_{i/o}$ proteins and PKC and/or PKA, thereby invoking an additional metabotropic action for KARs (Melyan et al., 2002, 2004, 2004; Grabauskas et al., 2007). As in the CA1, excitability of mouse CA3 PCs is also modulated by KARs through a metabotropic effect that dampens I_{AHPs} (Fisahn et al., 2005; Ruiz et al., 2005). This metabotropic activity is directly affected by auxiliary NETO proteins and it is absent in NETO 1 knock-out (KO) mice, indicating a role for NETO 1 in the correct functioning of somatodendritic KARs that affects glutamate release (Wyeth et al., 2014).

In their modulatory role, KARs control both GABA and glutamate release (see Rodríguez-Moreno and Sihra, 2007a, b, 2011b for review). Originally, ground-breaking work with hippocampal GABAergic synapses showed KAR-mediated depression of GABA release (Rodríguez-Moreno et al., 1997, 2000, 2000; Clarke et al., 1997), yet subsequent studies identified the possibility that KARs facilitate GABA release (Cossart et al., 2001). Indeed, KARs mediate both inhibitory (Vignes et al., 1998; Contractor et al., 2000, 2003; Contractor et al., 2000; Kamiya and Ozawa, 2000; Schmitz et al., 2000; Negrete-Díaz et al., 2006, 2007, 2012; Lyon et al., 2011; Andrade-Talavera et al., 2013; Falcón-Moya et al., 2019) and facilitatory modulation of glutamate release at synapses onto principal cells (Bortolotto et al., 1999; Lauri et al., 2001, 2003; Contractor et al., 2001; Rodríguez-Moreno and Sihra, 2004, 2013; Breustedt and Schmitz, 2004; Pinheiro et al., 2007; Scott et al., 2008; Andrade-Talavera et al., 2012, 2013; Falcón-Moya et al., 2018a). Presynaptic KARs also appear to modulate glutamate release at SC synapses onto somatostatin interneurons (Sun and Dobrunz, 2006; Sun et al., 2009) and at glutamatergic terminals onto CA3 interneurons (Lauri et al., 2005). While some of the actions of KARs in modulating neurotransmitter release have been proposed to be ionotropic for both GABA (Frerking et al., 1998; Cossart et al., 1998; Rodríguez-Moreno et al., 2000; Christensen et al., 2004; Maingret et al., 2005; Mulle et al., 2000; Cossart et al., 2001; Jiang et al., 2001; Mathew et al., 2008; Liu et al., 1999) and glutamate release (Schmitz et al., 2000, 2001, 2001; Kamiya and Ozawa, 2000; Kamiya et al., 2002; Lauri et al., 2003; Scott et al., 2008; Fernandes et al., 2009), a significant number of these activities involve metabotropic mechanisms. Here we describe the metabotropic actions of KARs involved in the facilitatory and inhibitory modulation of glutamate release at different synapses in different brain regions, as well as their possible physiological role, discussing these mechanisms in terms of G-protein and protein kinase involvement.

2. Metabotropic actions of KARs modulating glutamate release

2.1. Hippocampus

2.1.1. Depression of glutamate release at SC-CA1 synapses

In the hippocampus, where the major projection pathways are glutamatergic, KAR activated by the agonists KA or domoate depress glutamatergic transmission by a direct metabotropic action at SC-CA1 PC synapses of adult rats (Frerking et al., 2001). This KAR-mediated modulation was confirmed to be presynaptic based on a fluctuation and paired-pulse analysis (Fig. 1A and B, Box 1). KAR activation mediated a decrease in excitatory postsynaptic potentials (EPSP) amplitude that was prevented when G-protein activity was inhibited by N-ethylmaleimide (NEM) and PTX, indicating the metabotropic nature of this KAR activity. Interestingly, this modulation does not require a diffusible second messenger and the lack of involvement of a protein kinase cascade was evident through the effect of the protein kinase inhibitor H-7. In this process, it appeared that membrane-delimited beta gamma subunits of $G_{i/o}$ directly inhibited presynaptic Ca^{2+} channels to restrain glutamate release. Surprisingly, this depression of glutamate release was thought to converge on presynaptic inhibition mediated by adenosine and $GABA_B$ receptor activation. This effect is similar to that of ATPA that depresses glutamate release by activating GluK1 subunit-containing KARs, and which is in part occluded by prior activation of $GABA_B$ or adenosine receptors (Partovi and Frerking, 2006).

In addition, KAR activation by KA in SC terminals mediates a reduction in intracellular Ca^{2+} that is correlated with the inhibition of glutamate release (Kamiya and Ozawa, 1998). In these experiments, the presynaptic fibre volley was not affected by KA, suggesting that it was not in principle the consequence of reduced excitability of the nerve terminal. In slices, KA application typically produces an inward current that recovers quickly (in contrast to the slow recovery of excitatory postsynaptic currents (EPSCs), as observed in experiments where KA mediates a decrease in glutamate release (Chittajallu et al., 1996). These data suggest that SC nerve terminals express KARs that act metabotropically to reduce voltage-dependent Ca^{2+} channel activity and inhibit glutamate release.

During development, studies of SC-CA1 synapses in neonatal rats confirmed the metabotropic role of KARs in depressing glutamate release (Lauri et al., 2006; Sallert et al., 2007). In these experiments, KARs containing GluK1 subunits are tonically active and they inhibit glutamate release, an effect not observed when the slices were treated with PTX or PKC inhibitors. With maturation the tonic activation of these receptors is lost, indicating a role in synaptic maturation and in the control of the number of functional glutamatergic synapses (Vesikansa et al., 2007). Indeed, KAR activation at SC-CA1 synapses only inhibits glutamate release and no role for KARs in facilitating glutamate release has been found. These results indicate an important role of KARs in synaptic maturation and in the control of network oscillations during development. In this respect, it is interesting to note that GluK1-containing KARs increase the number of synapses and the

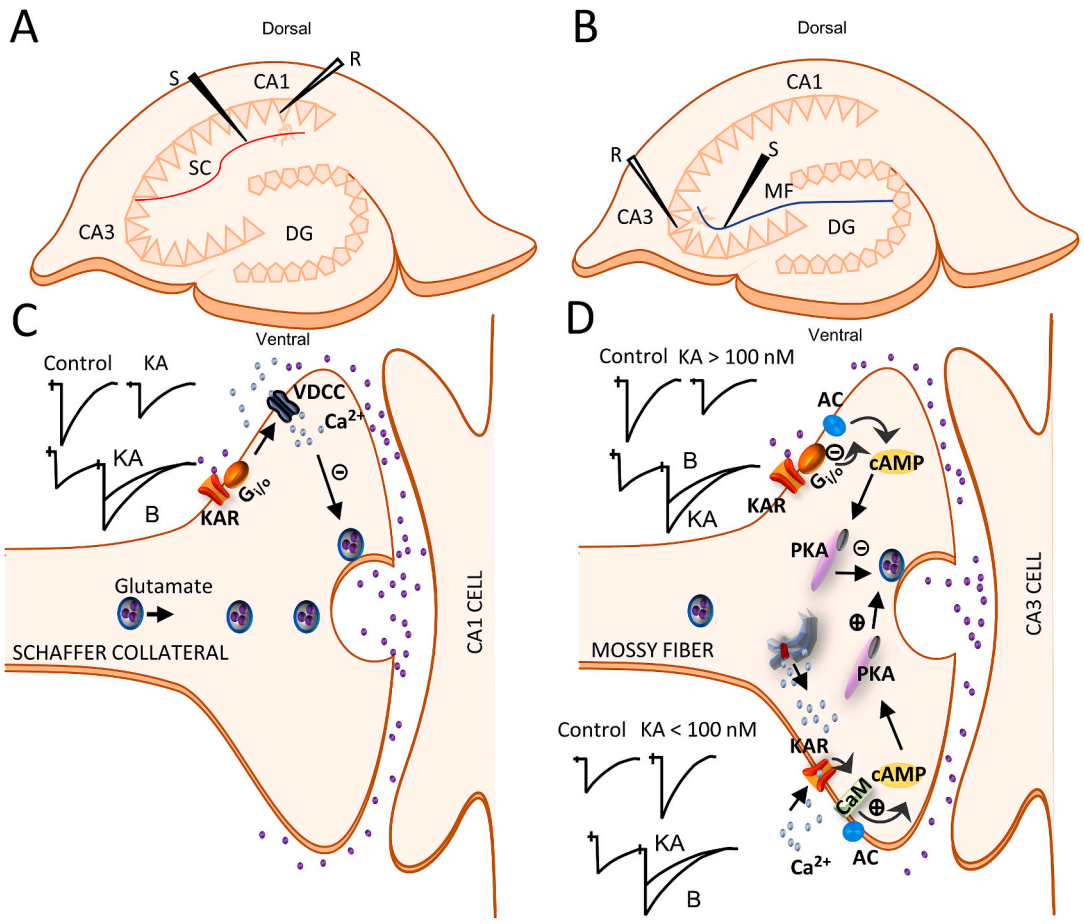


Fig. 1. Metabotropic actions of KARs in regulating glutamate release in the hippocampus. A, Experimental set-up for the experiments: S, stimulating electrode; R, recording electrode. B, Metabotropic actions of KARs at SC-CA1 pyramidal cell synapses. KAR activation mediates a depression of EPSC amplitudes at SC-CA1 synapses, which requires $G_{i/o}$-protein signalling and Ca^{2+} uptake through voltage-dependent calcium channels (VDCC) but not protein kinases. Paired-pulse traces show an increase in the paired-pulse ratio after exposure to KA (B, baseline; KA, kainate). C, D. Metabotropic action of KARs depressing and facilitating glutamate release at MF-CA3 synapses. C, Experimental set-up for experiments: S, stimulating electrode; R, recording electrode. KAR activation by high concentrations of KA depresses glutamate release at MF-CA3 synapses, an effect that involves a $G_{i/o}$ protein and the adenylate cyclase/cAMP/protein kinase A (AC/cAMP/PKA) pathway. KAR activation by low concentrations of KA facilitates glutamate release following activation of a Ca^{2+}-calmodulin/AC/cAMP/PKA pathway. Paired-pulse traces show an increase in the paired-pulse ratio after exposure to low [KA] and a decrease at high [KA] (B, baseline; KA, kainate).

frequency of excitatory miniature responses, an effect that is blocked by PKC inhibition (Vesikansa et al., 2007).

2.1.2. *Biphasic control of glutamate release by KAR activation at MF-CA3 synapses*

As indicated, KARs receptors exert bidirectional control over glutamate release at the MF-CA3 synapse (Fig. 1C and D): at low nanomolar concentrations KA (<50 nM) facilitates glutamate release (Contractor et al., 2000; Schmitz et al., 2001; Lauri et al., 2001, 2003, 2003; Rodríguez-Moreno and Sihra, 2004; Breustedt and Schmitz, 2004; Andrade-Talavera et al., 2012), whereas glutamate release decreases at high nanomolar concentrations (>100 nM: Kamiya and Ozawa, 2000; Schmitz et al., 2000; Contractor et al., 2001, 2003; Negrete-Díaz et al., 2006, 2007; Andrade-Talavera et al., 2012). The presynaptic nature of this modulation was indicated by the effect of KA application on paired-pulse facilitation (PPF), the number of eEPSC failures and the changes in the coefficient of variation ($1/CV^2$: Negrete-Díaz et al., 2006; Andrade-Talavera et al., 2012, Box 1).

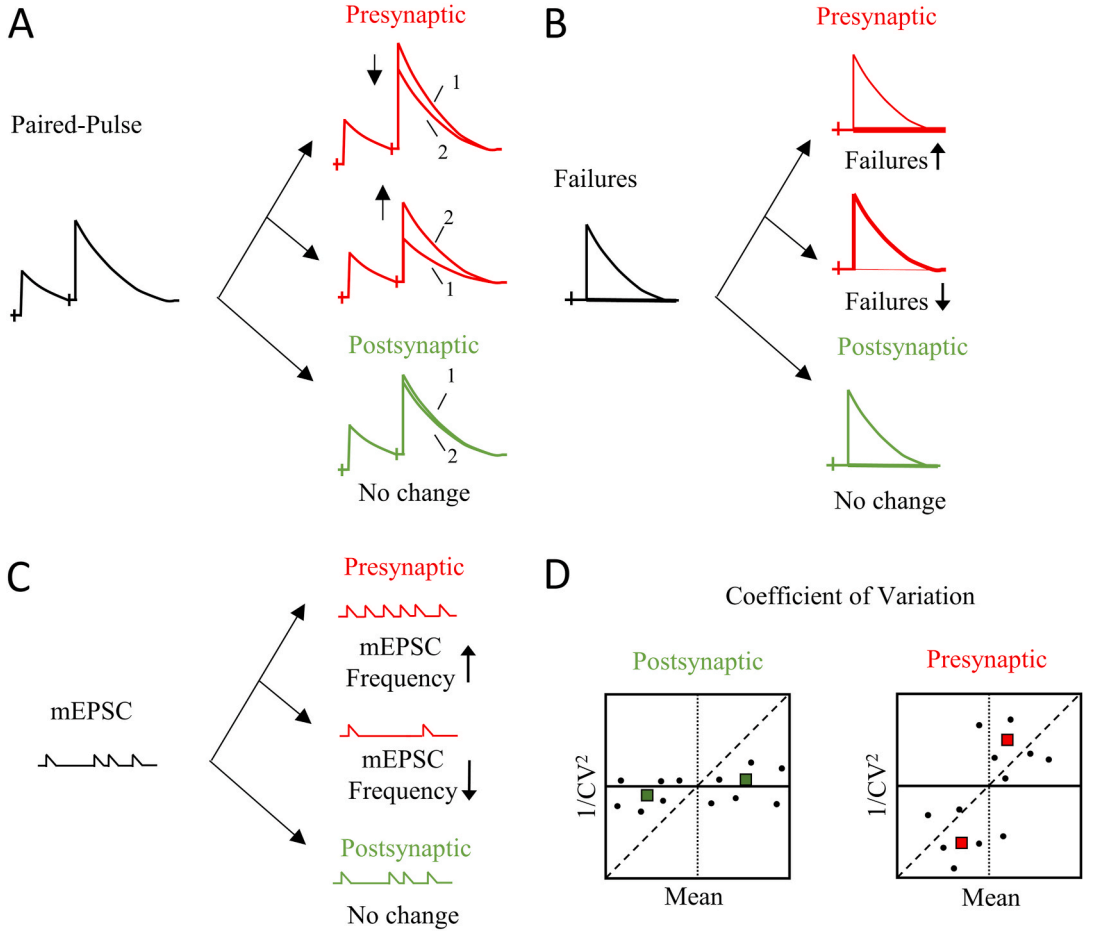
2.1.3. *Depression of glutamate release at MF-CA3 synapses*

The depression of glutamate release upon KAR activation by KA in slices from adult male mice has been defined as metabotropic at MF-CA3 synapses (Negrete-Díaz et al., 2006). The activation of KARs by high KA concentrations mediates a long-lasting depression with slow recovery, an effect that is not observed in the presence of PTX. In addition, inhibiting protein kinase A (PKA) with H-89 (catalytic inhibitor) or Rp-Br-cAMP (cAMP competitor), blocks the decrease in EPSC amplitude observed with KA. Thus, high KA concentrations activate KARs that interact with a $G_{i/o}$ protein, dampening the AC/cAMP/PKA cascade activity and causing a decrease in glutamate release (Negrete-Díaz et al., 2006).

A metabotropic role of KARs activated by endogenous glutamate or ATPA inhibiting glutamate release has been described at synapses onto CA3 pyramidal neurons of neonatal rats during development. This action is sensitive to PTX and PKC, and is similar to that in SC-CA1 synapses as KAR are tonically active to depress glutamate release (Lauri et al., 2005). With maturation, this tonic activation is lost, and whereas a PTX-sensitive G-protein is necessary for the depression of glutamate release during development and in adulthood, the depression of glutamate observed in adults requires PKA and the AC/cAMP/PKA pathway instead of PKC. However, the targets of PKA at these synapses are not yet known. Other studies have been performed at association/commissural (A/C)-CA3 pyramidal cells synapses. A/C terminals express KARs that depress glutamate release in a manner consistent with a metabotropic mechanism as no changes in fiber volley were observed while depressed fEPSP amplitude in a pertussis toxin dependent manner when activated

Box 1
Electrophysiological measurements and release probability.

The analytical approaches used to determine whether a mechanism involves a pre- or post-synaptic *locus* of action are supported by the quantal theory of synaptic release.



Analysis of failures and the paired pulse ratio (PPR). Synapses have a probability of not responding to a nerve stimulus, causing synaptic failure. If a presynaptic mechanism implies a greater probability of release, fewer failures in transmission would be expected. Conversely, if fewer events of neurotransmitter release are expected, the number of failures would increase (A). This is due to an increase or decrease in the amount of transmitter in the vesicles or changes in non-vesicular release. Such phenomena would not be expected from uniform changes in the number, sensitivity or conductance of receptor channels, or in the effectiveness of charge transfer form spines to dendrites (Malinow and Tsien, 1990). The same mechanism supports the paired-pulse ratio analysis (B). Synapses may present an increase or decrease in release after receiving more than one stimulus over a short time, establishing a release rate, therefore any modification in this ratio (either an increase or a decrease) would suggest that the origin is due to a modification of the release parameters of the presynaptic cell, in principle, ruling out a possible change in the post-synaptic origin. But changes in PPR may have alternative mechanistic explanations, like receptor desensitization or lateral diffusion (Heine et al., 2008; Constals et al., 2015).

Analysis of miniature postsynaptic responses: excitatory (mEPSCs) or inhibitory (mIPSCs). Even in the absence of nervous impulses, single neurotransmitter containing vesicles spontaneously fuse with specialized release sites in the presynaptic terminal, releasing their contents into the synaptic cleft through exocytosis. As a result, miniature postsynaptic responses are generated, which represent the postsynaptic response to the neurotransmitter contained in one vesicle. If changes are observed in the frequency but not in the amplitude of miniature postsynaptic responses, it would be expected that change was produced by a mechanism of presynaptic origin. Changes in amplitude but not in frequency of miniatures responses would indicate a postsynaptic mechanism, and changes in the frequency and the amplitude of those responses would be indicative of a mixture of presynaptic and postsynaptic changes (Manabe et al., 1992; C). Although the observation of changes in frequency/amplitude of mPSC is a reliable measure to determine a locus of action, there could be changes in mPSC frequency explained by changes in the number of functional synapses produced by silent synapses activation (Sametsky et al., 2010; Glasgow et al., 2018).

Analysis of the coefficient of variation (CV). The CV is defined as the ratio of the standard deviation to the mean. Based on the quantal model of neurotransmitter release this method establishes relationship between the ratios of the $1/CV^2$ (the inverse of the squared coefficient of variation), which defines the variance of the evoked responses and the amplitude of the postsynaptic responses before and after a particular experimental condition. Thus, changes in the amplitude of the postsynaptic responses followed by changes in $1/CV^2$ are normally indicative of a presynaptic locus of action (due to changes in the presynaptic release parameter: p, the probability of release; and N, the number of release sites). By contrast, changes in the amplitude of the synaptic responses in any experimental condition or treatment with no changes in $1/CV^2$ are normally indicative of a postsynaptic mechanism (due to changes in the parameter q, related to changes in postsynaptic amplitude of the synaptic responses because of changes in the postsynaptic parameters, D: discussed and reviewed in Brock et al., 2020).

by the selective GluK1 subunit-containing KARs agonist ATPA (Salmen et al., 2012).

Regarding the role of the depression of glutamate release at MF-CA3 synapses, reduced AC/cAMP/PKA activity associated with the decrease in glutamate release may be involved in synaptic plasticity at these synapses (Tzounopoulos et al., 1998). The KAR-mediated depression at MF-CA3 synapses is occluded by the prior induction of low-frequency stimulation (LFS)-mediated LTD. In addition, LTD induction is prevented by prior KAR-mediated depression in male mice (Negrete-Díaz et al., 2007) and LTD at MF-CA3 synapses is prevented by blocking KARs in Grm2/3 KO mice (Lyon et al., 2011).

2.1.4. Facilitation of glutamate release

Presynaptic KARs increasing glutamate release at MF-CA3 synapses were first described by Schmitz et al. (2001) showing that the activation of KARs by low KA concentrations (50 nM) increased the amplitude of NMDAR-mediated EPSCs. This increase involves a presynaptic locus of action for KA as a decrease in PPF was observed. This synaptic facilitation of glutamate release at MF-CA3 synapses has been observed when KARs are activated by either KA or by endogenous glutamate (Lauri et al., 2001, 2003, 2003; Ji and Staubli, 2002; Contractor et al., 2003; Rodríguez-Moreno and Sihra, 2004; Breustedt and Schmitz, 2004; Pinheiro et al., 2007; Scott et al., 2008; Andrade-Talavera et al., 2012), and has been proposed to require KARs containing GluK2 and GluK5 subunits (Contractor et al., 2000, 2003). Electrophysiological and biochemical studies on slices and hippocampal nerve terminals, demonstrated that the KAR-mediated increase in glutamate release at MF-CA3 synapses requires an increase in cytosolic Ca^{2+}, an event mediated by Ca^{2+} permeable KARs inducing Ca^{2+}-induced Ca^{2+}-release from internal stores (Lauri et al., 2003; Pinheiro et al., 2007; Scott et al., 2008; Andrade-Talavera et al., 2012, but see Kamiya et al., 2002).

Some years ago, we demonstrated that the increase in glutamate release mediated by presynaptic KARs when activated by KA in the rat hippocampus was driven by a mechanism involving AC/cAMP/PKA signalling (Rodríguez-Moreno and Sihra, 2004). This facilitatory mechanism requires the same intracellular cascade as the inhibitory action of KARs at MF-CA3 synapses, which is also mediated by the activation of an AC/cAMP/PKA cascade (Negrete-Díaz et al., 2006), although there is one fundamental difference as the increase in glutamate release mediated by KARs does not require G-protein activity, whereas the decrease in glutamate release clearly does (see Rodríguez-Moreno and Sihra, 2007a, b). Thus, G-protein independent activation of the AC/cAMP/PKA cascade in the hippocampus occurs through the increase in cytosolic Ca^{2+} produced by KAR activation, activating the Ca^{2+}-calmodulin that stimulates AC, either AC1 and/or AC8, the main Ca^{2+} stimulated ACs described in the CNS (see Wang and Storm, 2003; Cooper, 2003 for reviews). Interestingly, Ca^{2+}-calmodulin-mediated stimulation of ACs participates in long term potentiation (LTP), learning and memory processes (Cooper, 2003; Shan et al., 2008; Zhang et al., 2011), and KARs have been shown to participate in LTP at MF-CA3 synapses (Bortolotto et al., 1999; Contractor et al., 2001; Lauri et al., 2001, 2003, 2003; Schmitz et al., 2003; Breustedt and Schmitz, 2004). Together, these data suggest that KAR-mediated facilitation of glutamate release and the induction of LTP at MF-CA3 synapses share a common intracellular mechanism.

What is the role of this modulation of glutamate release at MF-CA3 synapses? KARs are expressed strongly at hippocampal MF-CA3 synapses (Represa et al., 1997; Darstein et al., 2003), where presynaptic KARs may pattern the physiological CA3 responses to the activation of granule cells (Henze et al., 2002). Incorrect spike transmission due to aberrant KAR activity may produce alterations in place cell activity and in defining spatial fields within the CA3 region, potentially affecting hippocampal-dependent behavioural tasks associated with CA3 activity (Kesner, 2007). As indicated above, KARs may fulfil an important role in LTP and LTD at MF synapses (Bortolotto et al., 1999; Contractor et al., 2001; Lauri et al., 2001; Schmitz et al., 2000, 2001, 2003, 2001;

Table 1
Summary of metabotropic actions of KARs modulating glutamate release.

	KAR-activation effect	G-protein	PKC	PKA	Possible Functions	Authors
Hippocampus						
SC-CA1						
Adult	Depression	Yes	No	No		Frerking et al. (2001), Partovi and Frerking (2006).
Neonate	Depression	Yes	Yes	?	Synaptic maturation, plasticity	Lauri et al. (2006) Saller et al. (2007) Vesikansa et al. (2007)
MF-CA3						
Adult	Facilitation	No	No	Yes	Plasticity	Rodríguez-Moreno and Sihra (2004); Negrete-Díaz et al. (2006); Lyon et al. (2011); Andrade-Talavera et al. (2012)
	Depression	Yes	No	Yes	Plasticity	
CA3 (A/C?)						
Neonate	Depression	Yes	Yes	?	?	Lauri et al. (2005)
Cultures		?	?	Yes	Synaptic maturation Vesicle mobilization	Gesolmino et al. (2013) Sakha et al. (2016)
Amygdala						
MGN-LA						
Adult	Depression	?	No	Yes	Plasticity, synaptic maturation	Negrete-Díaz et al. (2012). Ryazantseva et al. (2020)
Neonate	Facilitation	Yes	?	?		
Cerebellum						
PF-PuC	Facilitation	No	No	Yes	Neural maturation,	Falcón-Moya et al. (2018, 2019).
	Depression	Yes	No	Yes	Plasticity	
Neocortex						
Intracortical synapses	Facilitation	?	?	?	?	Campbell et al. (2007), Chamberlain et al. (2012)
	Depression	?	?	?		
Synaptosomes	Facilitation	No	?	Yes		Rodríguez-Moreno and Sihra (2013)
Thalamocortical	Facilitation	No	No	Yes	Plasticity	Andrade-Talavera et al. (2013)
synapses	Depression	Yes	No	Yes		
Globus pallidus	Depression	Yes	Yes	No	?	Jin et al. (2006)
Spinal cord						
DRG	Depression	Yes	Yes	?	Pain Neuronal maturation	Kerchner et al. (2001); Rozas et al. (2003) Marques et al. (2013)

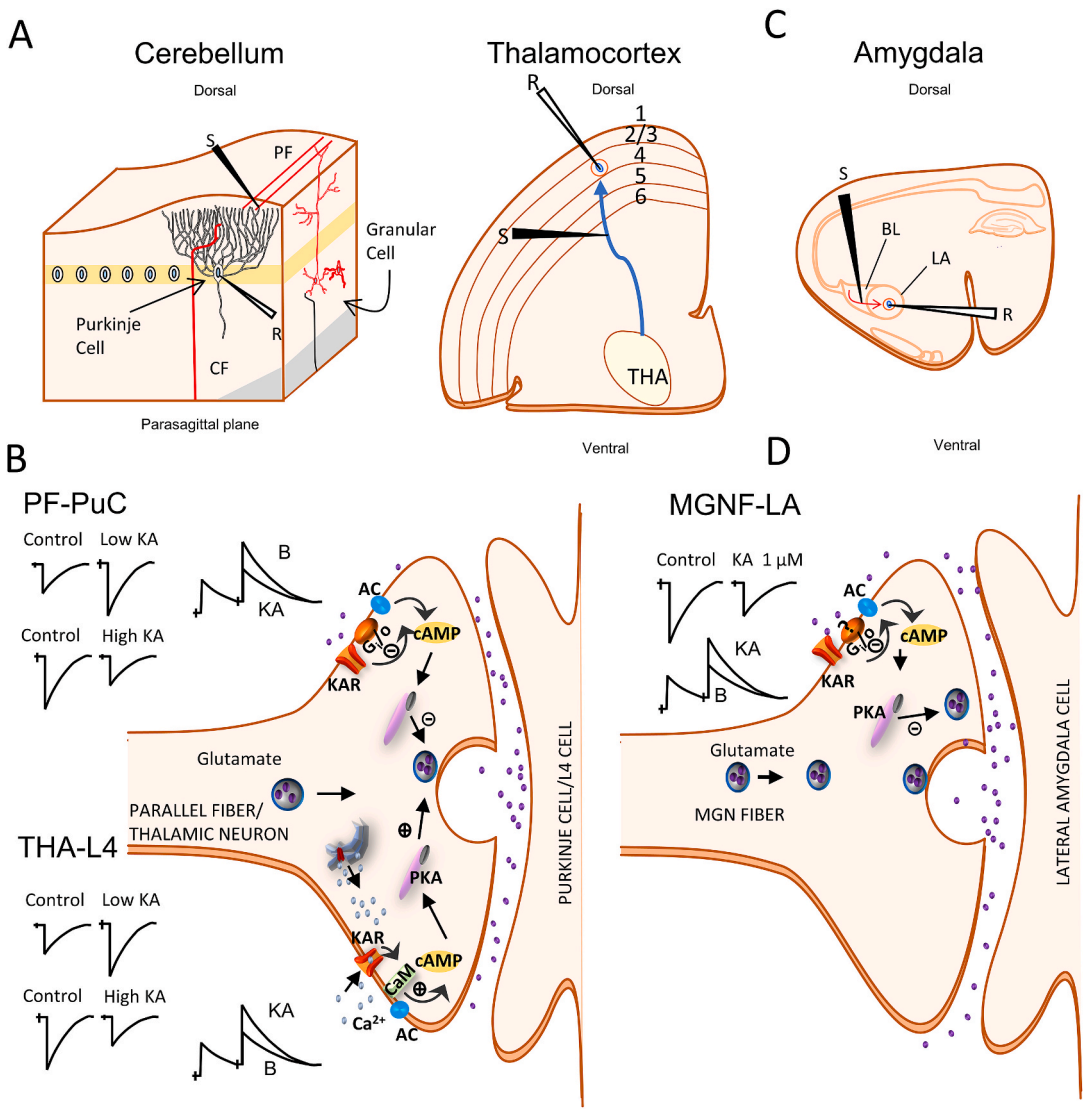


Fig. 2. KAR-mediated modulation of glutamate release in the cerebellum, at thalamocortical synapses and in the amygdala. A, Experimental set-up for studies in the cerebellum and thalamocortical synapses: S, stimulating electrode; R, recording electrode. B, Metabotropic actions of KARs at parallel fibre (PF)-Purkinje cell (PuC) and thalamic-Layer 4 (L4) synapses. KAR activation by high concentrations of KA depresses glutamate release at PF-PuC and thalamo-L4 synapses, an effect that involves a $G_{i/o}$ protein and the AC/cAMP/PKA pathway. KAR activation by low concentrations of KA only facilitates glutamate release following activation of a Ca^{2+}-calmodulin/AC/cAMP/PKA pathway. Paired-pulse traces show an increase in the paired-pulse ratio after exposure to low [KA] and a decrease at high [KA] (B, baseline; KA, kainate). C, Experimental set-up for studies in the amygdala: S, stimulating electrode; R, recording electrode; BL, basolateral amygdala; LA, lateral amygdala. D, Metabotropic actions of KAR at medial geniculate nucleus-lateral amygdala (MGN-LA) synapses. KAR activation by high concentrations of KA depresses glutamate release at MGN-LA synapses, an effect that involves the AC/cAMP/PKA pathway. The Paired-pulse traces show an increase in the paired-pulse ratio after exposure to KA.

Negrete-Díaz et al., 2007; Lyon et al., 2011; Nisticò et al., 2011; Andrade-Talavera et al., 2012). Moreover, the metabotropic actions of KARs during development modulate glutamate release and network activity in response to synaptic activation in the CA3 region of the hippocampus (Lauri et al., 2005). Interestingly, KA mobilizes presynaptic vesicles in hippocampal cultures in a manner that is dependent on PKA activation (Gesolmino et al., 2013). Indeed, presynaptic differentiation in these cultures required the assembly of scaffolding molecules, and subsequent G-protein and PKA-dependent phosphorylation of synapsin I, which affected the distribution of synaptic vesicles in the growth cone in response to KAR activation. In addition, KARs are involved in the control of axon growth and synaptic differentiation. For instance, low concentrations of KA enhance the motility of axonal filopodia in the developing hippocampus, whereas high concentrations have the opposite effect through a PTX sensitive mechanism (Tashiro et al., 2003). It may be possible that Ca^{2+} permeable axonal KARs strengthen efferent connectivity by increasing the density and differentiation of functional presynaptic release sites through mechanisms involving PKC and/or PKA (Sakha et al., 2016).

In conclusion, in the hippocampus KARs depress glutamate release at SC-CA1 synapses through a G-protein-dependent and protein kinase-independent mechanism (Fig. 1, Table 1). KARs play a biphasic role at MF-CA3 synapses, and KAR activation at low KA concentrations facilitates glutamate release mediated by a G-protein-independent, Ca^{2+}-calmodulin-AC/cAMP/PKA pathway. At higher KA concentrations, KAR activation depresses glutamate release through an AC/cAMP/PKA pathway that requires upstream G protein activity.

2.2. Amygdala

Facilitation (Li et al., 2001; Shin et al., 2010; Aroniadou-Anderjaska et al., 2012) and depression (Negrete-Díaz et al., 2012) of glutamate

release can be induced by pharmacological (either with KA or ATPA) or endogenous glutamate KAR activation in the amygdala. Mechanistically, a presynaptic AC/cAMP/PKA cascade mediates the depression of glutamate release when KARs are activated by KA at medial geniculate nucleus (MGN)-lateral amygdala nucleus (LA) synapses in slices from adult male mice (Negrete-Díaz et al., 2012). The effect of KA was not evident when cAMP/PKA signaling was prevented by treating slices with H-89 and Rp-Br-cAMP, yet it was evident when the slices were treated with calphostin C to block PKC activity (Fig. 2C and D; Table 1). It remains to be determined whether a G-protein is involved in this effect, as seen for the decreased glutamate release in the hippocampus (Frerking et al., 2001; Negrete-Díaz et al., 2006). The intracellular cascade involved in facilitating glutamate release mediated by KAR activation in the amygdala has not yet been determined and future studies will be necessary to define this. Interestingly, presynaptic KARs with a metabotropic role were recently described in amygdala slices from rats in their first postnatal week (Ryazanteva et al., 2020). At basolateral to central amygdala connections, presynaptic KARs containing the GluK1 subunit facilitated glutamate release by a mechanism involving G-protein coupling, which participates in the innervation and maturation of central amygdala neurons (Ryazanteva et al., 2020).

In terms of the possible role of KARs in the amygdala, this structure is known to participate in emotional behavior and learning, and it is important for the acquisition, storage and expression of conditioned fear memory (Ledoux, 2000). KARs may participate in these activities and thus, the weaker glutamate release induced by KARs may be protective, avoiding network oscillations that result in epileptogenic activity, as described in the hippocampus. In addition, it may combat seizure propagation (Khalilov et al., 2002; Schubert and Albrecht, 2008). Moreover, KARs are involved in LTP at these amygdala synapses (Shin et al., 2010), but whether they fulfil a role in LTD is not yet known. However, as KARs play a role in theta band oscillations in the amygdala, it is possible that when activated by very low concentrations of agonist, KARs might increase the oscillatory activity within this theta band (3–9 Hz, Sinfield and Collins, 2006).

2.3. Cerebellum

At parallel fiber (PF)-Purkinje Cell (PuC) synapses in the cerebellum, a biphasic activity of KARs modulating glutamate release has been described when activated by domoate (Delaney and Jahr, 2002), KA (Cervetto et al., 2010; Falcón-Moya et al., 2018a, 2019; Losada-Ruiz et al., 2019), or by synaptically released glutamate (Delaney and Jahr, 2002). Thus, like the MF-CA3 synapses, low KA concentrations enhance glutamate release while higher concentrations mediate depression. The facilitation of glutamate release by KARs is presynaptic, as it produced a decrease in the paired-pulse ratio (PPR) and in the number of failures of synaptic transmission, and it has the same effect over NMDA or AMPA mediated postsynaptic currents. KAR activation influences the facilitation of glutamate release and unless overridden by prior stimulation of adenylyl cyclase, this facilitation requires PKA activation as it is suppressed by inhibiting this kinase (Falcón-Moya et al., 2018a). KAR-mediated facilitation of synaptic transmission is prevented by blocking Ca^{2+} permeant KARs, and depletion of intracellular Ca^{2+} stores with thapsigargin or inhibition of Ca^{2+}-induced Ca^{2+}-release by ryanodine also prevented this synaptic facilitation. Thus, as in other synapses, KA-mediated modulation was conditional on extracellular Ca^{2+} entry through Ca^{2+}-permeable KARs and Ca^{2+} mobilization from intracellular stores. In addition, KAR-mediated facilitation is sensitive to calmodulin inhibitors, indicating that the increase in cytosolic [Ca^{2+}] that sustains KAR-mediated facilitation of synaptic transmission operates through downstream Ca^{2+}/calmodulin coupling. Thus, at cerebellar PF-PuC synapses in young adult male mice, presynaptic KARs can enhance synaptic transmission through Ca^{2+}-calmodulin dependent activation of AC/cAMP/PKA signaling, as found in the hippocampus and cortex (Falcón-Moya et al., 2018a: Fig. 2A and B; Table 1). Interestingly, facilitation was evident with a relative high agonist concentration (1–3 μM), whereas 500 nM agonist was previously found to depress glutamate release (Delaney and Jahr, 2002). This discrepancy may be due to the differences between the agonists (KA or domoate), ages and species used in the two studies. The depression of glutamate release after transient facilitation is also presynaptic as it increased the PPR and the number of failures, and it had the same effect on NMDAR and AMPAR mediated currents (Falcón-Moya et al., 2019: Box 1).

In accordance with previous studies in the hippocampus and amygdala (Negrete-Díaz et al., 2006, 2012), the inhibition of PKA cancels depression. Moreover, and unlike the mechanisms mediating the facilitation of glutamate release at the same synapse, and consistent with the findings in the hippocampus and amygdala regarding the depression of neurotransmitter release, KAR-mediated depression of glutamate release at PF-PuC synapses is impaired by inhibiting G protein activity with PTX. This effect does not appear to require Ca^{2+} entry into the cell through calcium permeable KARs or its release from internal stores as Ca^{2+} calmodulin is not necessary to activate AC (Falcón-Moya et al., 2019). Thus, like the facilitation of glutamate release, this depression involves the AC/cAMP/PKA pathway but not Ca^{2+}-calmodulin, as AC is activated by a $G_{i/o}$ protein to depress glutamate release (Fig. 2A and B; Table 1).

KARs act as autoreceptors at PF-PuC synapses, with the concentration of agonist defining presynaptic modulation (Delaney and Jahr, 2002; Cervetto et al., 2010), and potentially underlying synapse consolidation and stability. The expression of KAR subunits by immature granule cells in the outer germinal layer of the developing cerebellum suggests that KARs may also play a role in neuronal maturation. Although the precise role(s) of these KARs in adult animals remains to be elucidated, this modulation may be involved in some forms of plasticity, as synaptic refinement may involve glutamate receptors and KARs have been shown to be involved in plasticity at PF-PuC synapses (reviewed in Hirano, 2013). Presynaptic KARs participate in LTD at PF-PuC synapses, which is affected by the paired activation of climbing fibers (CFs) (Crépel, 2009). Of these two types of fibers that form synapses on the same PCs, PFs and CFs, only PFs have presynaptic KARs. This situation is similar to other brain regions, like the somatosensory and visual cortices, in which fibers with or without presynaptic glutamate receptors synapse onto the same postsynaptic cell and induce LTD (Buchanan et al., 2012; Banerjee et al., 2009, 2014). Exactly how KARs mediate LTD in the cerebellum is not yet clear and awaits further study. KARs have also been implicated in epilepsy (Falcón-Moya et al., 2018b) and whether this involves the cerebellum has yet to be determined. As KA injections are directly related to cerebellar ataxia, KARs may fulfil a direct role in ataxia (Maiti et al., 1986; De Vera et al., 2002; Yamaguchi et al., 1984; Andoh et al., 2008). Additionally, local KA injections in some areas of the cerebellum alter the levels of different ions, in particular affecting Ca^{2+} and inducing calcification (Korf and Postema, 1984; Savidge et al., 1997). However, whether this effect is directly mediated by the activation of KARs remains to be tested.

2.4. Neocortex

Presynaptic KARs activated by KA or ATPA enhance glutamate release in cortical areas (Perkinton and Sihra, 1999; Campbell et al., 2007; Chamberlain et al., 2012; Rodríguez-Moreno and Sihra, 2013), and like hippocampal MF-CA3 synapses and in the cerebellum, this KAR mediated facilitation involves a Ca^{2+}-calmodulin/AC/cAMP/PKA pathway but not a G-protein (Rodríguez-Moreno and Sihra, 2013). As occurs in the hippocampus (Andrade-Talavera et al., 2012) and cerebellum (Falcón-Moya et al., 2018a), this facilitation involves an increase in cytosolic Ca^{2+} and Ca^{2+} release from intracellular stores to activate Ca^{2+}-calmodulin, and subsequently the AC/cAMP/PKA pathway. This has also been observed in synaptosomes from male rats (Rodríguez-Moreno and Sihra, 2013); as they are only composed of functional presynaptic elements, this facilitation is clearly mediated by presynaptic

KARs (Fig. 2A and B; Table 1). Interestingly, a presynaptic form of LTP involving KARs and AC/PKA has also been described in the anterior cingulate cortex (ACC: Koga et al., 2015a).

In slices from mice, a biphasic effect of pharmacological KAR activation was found at synapses established between axons from the ventrobasal thalamus and L4 stellate neurons of the somatosensory cortex. This effect of KARs is presynaptic, as indicated by a fluctuation and paired-pulse analysis, and as the same effect was observed on NMDA or AMPA mediated postsynaptic currents. As for hippocampal MF-CA3 synapses, low KA concentrations mediate an increase in glutamate release and higher concentrations mediate depression (Jouhanneau et al., 2011; Andrade-Talavera et al., 2013). Similar results were obtained from synaptosomes and slices, and as in the hippocampus, facilitation and depression involved a AC/cAMP/PKA pathway, with facilitation requiring AC activation by Ca^{2+}-calmodulin and depression requiring PTX-sensitive G-protein activation (Andrade-Talavera et al., 2013: Fig. 2A and B; Table 1). KARs may be involved in the plasticity described at thalamocortical synapses during development (Kidd et al., 2002), and in the somatosensory integration and network activity observed in adults (reviewed in Feldman et al., 1999).

2.5. Other brain regions

In the globus pallidus of juvenile rats, a metabotropic effect to inhibit glutamate release is mediated by the activation of KARs by KA and it involves a $G_{i/o}$ protein. Interestingly, this metabotropic activity requires PKC but not PKA activity, as it was blocked with NEM or calphostin C but not with H-89 (Jin et al., 2006). KARs have not yet been proposed to enhance glutamate release in the globus pallidus.

In juvenile mice of either sex, GluK2-containing postsynaptic KARs expressed by direct pathway spiny projection neurons dampen glutamate release in corticostriatal synapses in the dorsolateral striatum. Here, when postsynaptic KARs are activated by KA they have been proposed to metabotropically increase cannabinoid release, and activating presynaptic CB_1 receptors indirectly inhibits glutamate release (Marshall et al., 2018).

In spinal cord cell cultures from mice and rats, activation of GluK1 subunit-containing KARs dampens glutamate release (Kerchner et al., 2001) in a G-protein dependent manner (Rozas et al., 2003). In dorsal root ganglion (DRG) neurons, low KA concentrations promote neurite extension by a mechanism that involves metabotropic KAR activity, resulting in CRMP2 phosphorylation. By contrast, higher KA concentrations prevent neurite extension by an ionotropic mechanism (Marques et al., 2013).

In summary, the activation of KARs produces either depression or facilitation of glutamate release in different brain regions. When depression is observed, it requires G-protein activation, with one case of a protein kinase-independent, membrane-delimited, mechanism, yet in all other cases involving protein kinase activity. This protein kinase is PKA in most cases, involving PKC in others. PKA activation involves an AC/cAMP/PKA pathway. KARs that dampen glutamate release via a metabotropic action participate in maturation during development and in the trafficking of vesicles, and they may play a role in LTD as well as fulfilling a protective role in preventing the oscillations that lead to epileptic seizures. The activation of KARs by low agonist concentrations mediates an increase in glutamate release that does not require G protein activity, and in most cases it involves the Ca^{2+}-calmodulin/AC/cAMP/PKA pathway. KARs mediating an increase in glutamate release may influence maturation and LTP, as well as other forms of plasticity.

3. Future research

Significant advances have been made in recent years in establishing the metabotropic actions of KARs involved in modulating glutamate release. The mechanisms and intracellular cascades emerging are the same at different synapses and in different brain areas. In addition, although some advances have been made in elucidating the specific role of these intracellular cascades in particular activities in the CNS, there is still much to be learnt. We have indicated possible functions of KARs in each brain region but there are still aspects of their behaviour that require study, as indicated below.

a) *The substrates phosphorylated when the metabotropic signalling cascades involved in modulating glutamate release are activated and the functions they fulfil.* Some of the PKA and PKC substrates seen to be phosphorylated after KAR activation are involved in vesicle mobilization in growth cones (Gesolmino et al., 2013), neurite outgrowth and axonal filopodia regulation (Chang and De Camilli, 2001; Tashiro et al., 2003; Ibarretxe et al., 2007; Joseph et al., 2011; Marques et al., 2013), although the information available remains limited. KARs themselves are potential targets of kinases and indeed, the GluK2 subunits of KARs are known to be modulated by PKA. Indeed, KA currents are potentiated by intracellular perfusion of PKA (Wang et al., 1993; Kornreich et al., 2007). Although, most of the cloned glutamate receptor subunits contain potential phosphorylation sites for PKC and Ca^{2+}-calmodulin-dependent protein kinase II, only the GluK2 subunit contains a consensus sequence site for PKA phosphorylation (Swope et al., 1992; Kennelly and Krebs, 1991). Additionally, axonal KARs regulating presynaptic differentiation involving PKA and PKC have been described in axons isolated microfluidically (Sakha et al., 2016). It remains to be determined whether more substrates are phosphorylated after KAR activation in different brain regions, either by PKA or PKC, and the roles they may play.

b) *Subcellular location of KARs that metabotropically mediate a decrease or increase in glutamate release.* At different synapses, it is important to determine whether the metabotropic modulation of glutamate release observed by the activation of presynaptic KARs is mediated by receptors on axons or in the somatodendritic compartment. The exact subcellular location of the KARs at different synapses is still to be defined and will require direct approaches to be adopted. For instance, immunogold-based receptor localization studies should be carried out using specific KAR antibodies. Moreover, caged blockers of KARs should be developed, as used to study the distribution of NMDARs (Rodríguez-Moreno et al., 2011; Reeve et al., 2012) in conjunction with paired-recordings between pre- and postsynaptic neurons (Rodríguez-Moreno and Paulsen, 2008; Banerjee et al., 2014; Rodríguez Moreno et al., 2010; Rodríguez-Moreno et al., 2013). The development and use of agonists and antagonists in the patch-pipette that act intracellularly would be a useful tool. Indeed, the postsynaptic metabotropic actions of KARs modulating I_{AHPs} and cell excitability may affect glutamate release in the postsynaptic cell. These postsynaptic metabotropic actions have been found at two types of hippocampal synapses. It will be of great interest to determine whether this type of modulation also occurs at other synapses and in different brain regions, and to determine the true effect on network activity, not only during development but also in adulthood. In addition, whether presynaptic axonal metabotropic KARs and postsynaptic metabotropic KARs modulating neuronal excitability are activated by glutamate at the same time, having a simultaneous effect on presynaptic and postsynaptic glutamate release should also be addressed. It will also be of interest to gain more information related to the role of the auxiliary NETO proteins in glutamate release and how they affect the function of somatodendritic KARs.

c) *Endogenous activation of KARs and new agonist/antagonists.* Many of the studies described here only involved the pharmacological activation of KARs by agonists like KA or ATPA. Thus, whether the endogenous agonist of these receptors, glutamate, produces the exact same effects on glutamate release by activating KARs remains to be established at all synapses. Finally, the development of new and more specific agonists and antagonists for KARs containing specific subunits will be important to determine the subunit composition of

different KARs modulating glutamate release and to selectively treat defects in KAR activity.

d) *How do KARs couple to G proteins when G-proteins are required for their modulation?* As KARs do not have a known G protein-binding motif, an intermediary protein was first proposed to mediate this interaction (Rodríguez-Moreno and Lerma, 1998; Cunha et al., 1999). However, a direct interaction between GluK1 and G_o protein has since been indicated by proteomics analysis (Rutkowska-Wlodarczyk et al., 2015), similar to the PTX sensitive G protein coupling to KARs found previously (Ziegra et al., 1992; Cunha et al., 1999). Moreover, a direct biochemical interaction between GluK5 and Gαq had also been identified earlier (Ruiz et al., 2005). A polybasic stretch present in the CDT domain of different receptors facilitates their interaction with G proteins (Qin et al., 2011), and the GluK1, GluK2 and GluK5 subunits have a similar motif, suggesting possible interactions between the KAR CDT domain and G proteins. However, the mechanisms underlying the direct interaction between KARs and G proteins remain to be determined, as well as the proteins that may potentially couple KARs to G proteins. Hence, this important issue should be studied in more depth.

e) *The role of metabotropic presynaptic KARs modulating glutamate release in plasticity.* Postsynaptic mKARs have been implicated in hippocampal plasticity (Selak et al., 2009; Paternain et al., 2000; Petrovic et al., 2017) and a role for presynaptic KARs with metabotropic actions has been proposed in the presynaptic LTD at MF-CA3 synapses (Negrete Díaz et al., 2007; Lyon et al., 2011) and in the LTP and LTD expression in the area CA1 early during development (Clarke et al., 2014). It will be interesting to study the role of metabotropic KARs in modulating glutamate release associated with synaptic plasticity in other brain regions.

f) *The role of the metabotropic modulation of glutamate release in network oscillations.* Together with the modulation KARs exert on GABA release, the modulation of glutamate release may directly affect the excitatory/inhibitory balance and thus, significantly affect cell physiology. The effects of KAR activation on the excitation/inhibition balance, and on the intracellular cascades involved, remains to be determined in network oscillations and in behavioural paradigms. Epilepsy represents a clinically relevant consequence of the modulation of glutamate release and of an altered excitatory/inhibitory balance. As distinct forms of epilepsy could potentially be provoked by presynaptic KARs, this should be studied in more detail.

g) *Is KAR-mediated metabotropic modulation of glutamate release affected by the modulation of glutamate release exerted by other glutamate receptors?* From the information available from different glutamate receptors, it is now clear that different receptors control glutamate release in presynaptic terminals/axons. Thus, KARs, NMDARs and mGluRs may be present in the same terminals, and each may influence glutamate release. Indeed, KARs, NMDAR and mGluRs have been reported to each modulate glutamate release in the SC-CA1 region of the hippocampus (Rodríguez-Moreno et al., 1998; Frerking et al., 2001; Lauri et al., 2006; Sallert et al., 2007; Prius-Mengual et al., 2019; Pérez-Rodríguez et al., 2019; Falcón-Moya et al., 2020), and these receptors may cooperate to depress or facilitate glutamate release, or produce antagonistic effects, or they may even act independently as they could be located at different sites, e.g., synaptic or extrasynaptic. For instance, KARs and mGluR have been described as having a synergistic interaction in MF LTP (Nisticò et al., 2011). Interestingly, KARs, NMDARs and mGluRs are present at SC-CA1 synapses, and they are tonically activated by endogenous glutamate (Rodríguez-Moreno et al., 1998; Lauri et al., 2006; Prius--Mengual et al., 2019; Pérez-Rodríguez et al., 2019). Whether they are active at the same time by the amount of glutamate normally present in the synaptic cleft is not clear at present and thus, how many presynaptic glutamate receptors are simultaneous active at different synapses and whether they affect the activity of the rest needs to be investigated to unequivocally determine under what conditions NMDARs, AMPARs, KARs and mGluRs are activated by endogenous glutamate. It is also interesting to note that while there is abundant evidence that the presynaptic KARs that modulate glutamate release fulfil metabotropic actions, the amount of information related to the existence of presynaptic metabotropic NMDARs is quite limited (Abrahamsson et al., 2017; Bouvier et al., 2018). Indeed, the known presynaptic actions of NMDARs that modulate glutamate release are assumed to be basically ionotropic.

h) *Do alterations to metabotropic KARs mediate the modulation of glutamate release involved in brain diseases?* KARs are emerging as possible targets to combat different diseases. In relation to glutamate release, a form of presynaptic LTP in the ACC in which KARs participate in wild-type animals requires PKA and it is not evident in fragile X mental retardation (*Fmr*1) KO mice (Koga et al., 2015b). Hence, it would be interesting to determine how human mutations affect glutamate release and the role of PKA (or PKC when involved) in these phenomena. It is also known that *Grik*2 gain of function causes developmental deficits, changing an alanine codon at position 657 in the GluK2 KAR subunit for threonine (A657T) alters receptor functioning and makes it active in almost glutamate-free extracellular media (Guzmán et al., 2017). Clearly, more work is necessary to determine the exact roles of KARs in the metabotropic modulations of glutamate release and the consequences of altering their behaviour. While genetic studies are of great interest, most of the physiological consequences of genetic deficits are unknown for the moment and need to be determined in terms of the presynaptic and postsynaptic activity of KARs.

Author's contributions

All the authors contributed to the design and writing of the review.

Declaration of competing interest

The authors have no conflict of interests to declare.

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