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Kainate receptors, homeostatic gatekeepers of synaptic plasticity

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Abstract – Extensive research over the past decades has characterized multiple forms of synaptic plasticity, identifying them as key processes that allow the brain to operate in a dynamic manner. Within the wide variety of synaptic plasticity modulators, kainate receptors are receiving increasing attention, given their diversity of signaling mechanisms and cellular expression profile. Here, we summarize the experimental evidence about the involvement of kainate receptor signaling in the regulation of short- and long-term plasticity, from the perspective of the regulation of neurotransmitter release. In light of this evidence, we propose that kainate receptors may be considered homeostatic modulators of neurotransmitter release, able to bidirectionally regulate plasticity depending on the functional history of the synapse.

Key words – kainate receptors, hippocampus, synaptic plasticity, long-term potentiation, long-term depression, homeostatic plasticity.

INTRODUCTION

The identification of glutamate as a powerful proconvulsive agent (Hayashi, 1954) inaugurated the search for specific receptors activated upon binding of this amino acid. Several decades after, different putative types of receptors had been described thanks to the use of pharmacological tools (e.g. Curtis and Watkins, 1960; Shinozaki and Shibuya, 1974; Krogsgaard-Larsen et al., 1980), but it was the advent of the cloning era that finally resulted in an unambiguous classification of the different proteins composing ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs, respectively, see Traynelis et al., 2010;

Niswender and Conn, 2010 for reviews). Within iGluRs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate receptors (AMPARs and NMDARs, respectively) have attracted most of the attention, given that they convey the vast majority of excitatory neurotransmission and constitute the main molecular players in most synaptic plasticity processes. On the other hand, a third subfamily of iGluRs, the kainate receptors (KARs) have received much less attention, even in spite of the prominent aspects of their biology that endow them with the capacity to modulate a wide variety of synaptic and cellular processes such as neuronal development, synaptic depolarization and intrinsic cell excitability (reviewed in Lerma and Marques, 2013). In this review, we will focus on the presynaptic actions of KARs, especially those related with the modulation of plasticity processes in the context of their diverse signaling mechanisms.

General aspects of KARs biology

The five members of the KARs family (named GluK1 to GluK5) are further classified in two subfamilies, the so-called low- and high-affinity. GluK1 to GluK3 compose the low-affinity subunits, whose activation requires higher concentrations of glutamate or kainic acid (KA) and can form homomeric receptors, whereas GluK4 and GluK5 are the members of the high-affinity subfamily, can be activated by lower concentrations of agonist and require heteromerization with any of the low-affinity subunits for cellular membrane delivery. Alternative splicing of GluK1 to GluK3 and editing of GluK1 and GluK2 mRNAs further enhance the repertoire of KARs (see Lerma et al., 2001 for a review). The functional diversity of these receptors is increased by the different combinations of subunits present in KARs at a wide variety of synapses. In the hippocampus, the brain area that has received most attention in the study of these receptors, the GluK2 and GluK5 subunits are present at the majority of principal cells and different types of interneurons, whereas the expression of other subunits varies between cell types, synapses and developmental stages (Paternain et al., 2000). Thus, GluK1 is widely expressed during development whereas, in the adulthood, it is mostly restricted to interneurons in the hippocampus (Paternain et al., 2000; Vesikansa et al., 2007). GluK3 is almost exclusively expressed in dentate gyrus (DG) granule cells (Pinheiro et al., 2007)

and GluK4 is mainly present in DG and CA3 pyramidal neurons, showing consistent although reduced levels of expression in interneurons and CA1 pyramidal cells (Arora et al., 2018).

KARs, the special iGluRs

As we stated above, KARs present prominent characteristics that make them interesting contributors to the modulation of a variety of processes. On one hand, KARs have proven to be special iGluRs regarding to their signaling capacities. Thus, the canonical mode of action of these receptors involves the opening of an ion channel pore upon agonist binding. Interestingly, in contrast to AMPARs, KAR-mediated currents are small in amplitude and present slow activation and deactivation kinetics (Castillo et al., 1997; Vignes and Collingridge, 1997; Frerking et al., 1998). This slow kinetics is bestowed by Neto proteins as auxiliary subunits of KARs (Zhang et al., 2009; Straub et al., 2011; Lerma, 2011; Palacios-Filardo et al., 2016) and endow them with the ability to modulate short-term plasticity, input integration and brain rhythms (Frerking and Ohliger-Frerking, 2002; Goldin et al., 2007; Straub et al., 2011; Sylwestrak and Ghosh, 2012). On the other hand, KARs can activate a so-called non-canonical signaling pathway through an archetypal metabotropic cascade involving a G_o protein, phospholipase C (PLC) and protein kinase C (PKC) (Rodríguez-Moreno and Lerma, 1998; Cunha et al., 2000; Rozas et al., 2003). The activation of such non-canonical pathway has been demonstrated for every family of iGluRs (see Valbuena and Lerma, 2016 for a review) but, whereas AMPARs and NMDARs perform their actions mainly through ionotropic means, metabotropic signaling by KARs constitutes a pivotal mechanism in part of their physiological roles (Rodríguez-Moreno and Lerma, 1998; Frerking et al., 2001; Melyan et al., 2004; Marques et al., 2013). While the non-canonical signaling functions of KARs are now relatively well characterized, the mechanism by which KARs activate this pathway is still largely obscure. The structure of iGluRs does not contain any known motif similar to those allowing interaction between mGluRs and G-proteins, so it has been proposed that an adaptor protein may bridge the activation of KARs and G_o (Rodríguez-Moreno and Lerma, 1998). However, different reports highlight that specific subunits of KARs may directly interact with

G-proteins, although the binding mechanism remains unknown (Ziegra et al., 1992; Cunha et al., 1999; Rutkowska-Wlodarczyk et al., 2015).

A second interesting aspect of KARs biology deals with their subcellular location. As other iGluRs, KARs are preferentially expressed in postsynaptic regions. However, whereas AMPARs and NMDARs are only sporadically present at presynaptic compartments in specific synapses (e.g. Takago et al., 2005; Dubois et al., 2016), presynaptic KARs are unusually common (Rodríguez-Moreno et al., 1997; Kamiya and Ozawa, 1998; Schmitz et al., 2001b). This fact, together with the rich diversity of KARs subunit combinations in different excitatory and inhibitory synapses (Lauri et al., 2001a; Christensen et al., 2004; Pinheiro et al., 2007; Wyeth et al., 2017) has resulted in the description of a wide variety of effects caused by the action of these presynaptic receptors. Altogether, the combination of the multiplicity of signaling mechanisms and their widespread location in presynaptic compartments makes KARs ideal candidates for regulating plasticity mechanisms –especially at the short-term-.

KAINATE RECEPTORS REGULATE SHORT-TERM PLASTICITY

Regulation of glutamate release and plasticity in CA3

Whereas the involvement of KARs in glutamate release from CA3 synaptic terminals is now well established (see below), severe discrepancies remain regarding the role of KARs in the control of glutamate release from mossy fibers (MF). These synapses constitute one of the main inputs into the hippocampus proper and have been widely studied due to their particular morphology and synaptic plasticity properties. Thus, MF-CA3 synapses present multiple release sites and a low probability of release, two factors that make them specially suitable to undergo short-term plasticity processes, that in turn confer them the capacity to act as “conditional detonators” which reliably generate action potentials in CA3 cells, but only upon high frequency burst activation (Henze et al., 2002). Different forms of short-term plasticity (STP) have been described in MF-CA3 synapses, being paired-pulse facilitation (PPF), frequency facilitation (FF) and post-tetanic potentiation (PTP) the most prominent ones (see Nicoll and Schmitz, 2005 for a review).

The involvement of KARs in the physiology of MF-CA3 synapses has been profoundly studied over more than two decades. These receptors were first described in the postsynaptic site of MF-CA3 synapses (Castillo et al., 1997; Vignes and Collingridge, 1997), but shortly after it was reported a role for presynaptic KARs in the regulation of glutamate release in this area, as the application of the GluK1 specific agonist ATPA reduced the amplitude of excitatory postsynaptic currents (EPSCs) evoked upon MF stimulation (Vignes et al., 1998; Bortolotto et al., 1999). Further studies evaluated this possibility, and it was found that KA could decrease the Ca^{2+} entry in the presynaptic site of MF and, concomitantly, reduce the amplitude of the evoked EPSC and field excitatory postsynaptic potential (fEPSP, Kamiya and Ozawa, 2000). A KAR-mediated facilitation of glutamate release from MF was also proposed, as the application of low KA concentrations resulted in an increase of the EPSC amplitude in these synapses (Schmitz et al., 2001b; Contractor et al., 2003; but see Pinheiro et al., 2007; Kwon and Castillo, 2008). Such bimodal action of KARs at low and high KA concentrations would rely on the participation of different subunits as the former, but not the later, was lost upon genetic ablation of the GluK5 encoding gene *Grik5* (Contractor et al., 2003). On the other hand, both the KAR-dependent increase and reduction in the amplitude of EPSC in MF-CA3 synapses may depend on GluK2 (Contractor et al., 2000). The involvement of the GluK1 subunit in any of these effects is still a strong point of controversy, as pharmacological and knock-out mice data are contradictory. The debate regarding the involvement of GluK1 in the regulation of glutamate from MF has continued over years, with data pointing to and against the participation of this subunit (Contractor et al., 2000; 2001; Schmitz et al., 2000; Lauri et al., 2001b).

The obvious consequence of the KAR-mediated modifications in glutamate release from MF is the regulation of STP in these synapses. It has been shown that low concentrations of KA can reduce PPF in MF-CA3 synapses by enlarging the response to the first stimulus (Schmitz et al., 2001b), an effect consistent with the enhancement in EPSC amplitude described above. The participation of KARs in the modulation of PPF has also been reported in the absence of exogenous KAR activation. Thus, $GluK2^{-/-}$ mice present reduced PPF, in this case as a consequence of the reduction of the amplitude of the response to the second

pulse, suggesting that this subunit may be required for the prominent PPF present in these synapses (Contractor et al., 2001; Schmitz et al., 2001a; Breustedt and Schmitz, 2004; but see Kwon and Castillo, 2008). The participation of GluK3 in the modulation of this process has also been reported (Pinheiro et al., 2007). On the other hand, KARs may modulate FF in MF-CA3 synapses. Application of the broad AMPAR and KAR blocker CNQX resulted in a reduction of the FF in these synapses (Schmitz et al., 2001b), and this form of STP is attenuated in GluK2 and GluK3$^{-/-}$ mice (Contractor et al., 2001; Pinheiro et al., 2007; but see Kwon and Castillo, 2008). The involvement of GluK1 in PPF and FF has also been proposed on the basis of pharmacological data (Lauri et al., 2001b) although, again, these results have been challenged by the use of GluK1$^{-/-}$ mice (Contractor et al., 2001). The participation of the high affinity subunits in PPF and FF has also been evaluated and, whereas neither GluK4$^{-/-}$ nor GluK5$^{-/-}$ mice present deficits in STP, the double KO mouse presents impaired PPF but spared FF, suggesting that these two plasticity processes may rely on different mechanisms (Contractor et al., 2003; Fernandes et al., 2009).

From a mechanistic perspective, it has been proposed that both the facilitation and the depression of glutamate release from MF rely on the activation of KARs ionotropic pathway. This hypothesis was postulated upon the evaluation of the effects that low and high concentrations of KAR agonists have in the fiber volley recorded upon MF stimulation (Kamiya and Ozawa, 2000; Schmitz et al., 2000; Schmitz et al., 2001b). Thus, low concentrations of KAR agonists would depolarize the terminal by Na^+ or Ca^{2+} permeation facilitating glutamate release, whereas high concentrations would further depolarize the terminal inactivating voltage-dependent Na^+ and/or Ca^{2+} channels and, therefore, depressing glutamate release (Schmitz et al., 2001b). Overall, even though important controversies hamper definitive conclusions, it is conceivable that KARs may act as gatekeepers at MF-CA3 synapses, being their effect on release dependent on the concentration of glutamate –i.e. in a synapse-autonomous manner.

Regulation of glutamate release and plasticity in CA1

The first description of a KAR effect in glutamate release was its KA-mediated reduction in the CA1 area (Chittajallu et al., 1996). Chittajallu and colleagues reported a role of KA in the depression of glutamate release evoked by 4-AP and K^+ in hippocampal synaptosomes. Then they evaluated the action of KA in CA3-CA1 synapses, finding a similar effect upon exposure to high concentrations of KA. Thus, high concentrations of this agonist depressed NMDAR EPSCs in the presence of adenosine and $GABA_B$ receptors antagonists. The effect was spared in the presence of BAPTA in the recording pipette, excluding the participation of postsynaptic Ca^{2+}, and was mimicked by domoic acid (DA), another KAR agonist, but not AMPA. Finally, the effect was blocked by previous application of the KAR antagonist NS-102. Interestingly, low concentrations of KA evoked an opposite effect (similar to that presented above in the CA3 area), enhancing the CA3-CA1 NMDAR EPSC.

Subsequent studies have further characterized the inhibitory action of KARs on the release of glutamate at CA3-CA1 synapses. Thus, it has been reported that 1 μM KA can reversibly depress the fEPSP recorded at the CA1 stratum radiatum. Such effect was accompanied by a reduction in the Ca^{2+} entry at the presynaptic compartment and could be mimicked by DA. Again, there was an increase in the PPF (in this case of the fEPSP). Both the AMPAR-mediated and the NMDAR-mediated EPSCs were affected although, intriguingly, the effect was more prominent over the AMPAR component (Kamiya and Ozawa, 1998). The effect has been ascribed to the GluK1 subunit of the KAR receptor, as it has been shown that the GluK1-specific agonist ATPA was enough to reduce the slope of the fEPSP. Furthermore, the effect of this agonist was prevented by the application of the GluK1-specific antagonist LY382884 (Vignes et al., 1998). Finally, in a beautiful paper, Frerking and colleagues showed that KARs effect was not mediated by ionotropic but metabotropic signaling, as it was blocked by pertussis toxin, a G-protein inhibitor (Frerking et al., 2001). Furthermore, the authors showed that the effect was likely due to the direct interaction of βγ subunits of G-protein, as the protein kinase inhibitor H-7 did not have an effect on the KAR agonists-mediated reduction in EPSC. Similar results were obtained in a different study, which also showed that the effects of ATPA and DA on glutamate release from Schaffer collaterals (the axons of CA3 pyramidal cells)

may be exerted by KARs composed by different subunits, as UBP302, an inhibitor presenting selectivity over GluK1-containing KARs, was able to block the effect of the former, but not the later, agonist (Partovi and Frerking, 2006). This study showed, furthermore, that the signaling mechanisms used by KARs to reduce glutamate release from Schaffer collateral terminals were shared with adenosine and $GABA_B$ receptors, as agonists for these receptors occluded the posterior effect of KAR agonists.

Regulation of GABA release

KAR-mediated control of neurotransmitter release and plasticity is not restricted to the glutamatergic system. Whereas the expression profile of some subunits, such as GluK2 and GluK5 is widespread, the expression of GluK1 is almost completelly restricted to interneurons in the adult hippocampus (Paternain et al., 2000). Over the past decades, different studies have evaluated the expression of functional KARs in inhibitory cells, finding that these receptors can be expressed both at the somatodendritic and the axonal/presynaptic compartments (Cossart et al., 1998; Frerking et al., 1998; Cunha et al., 2000). As in the case of glutamate release, presynaptic KARs have been shown to bidirectionally modulate the release of GABA. Thus, it has been reported that high concentrations of KA can reduce the release of this neurotransmitter from hippocampal synaptosomes (Cunha et al., 1997). At the same time, a KAR-mediated reduction in GABA release over CA1 pyramidal neurons was described (Rodríguez-Moreno et al., 1997). Such reduction has been repeatedly reported afterwards (Frerking et al., 1998; Bureau et al., 1999; Cunha et al., 2000) and depends on the activation of the non-canonical signaling pathway of KARs (Rodríguez-Moreno and Lerma, 1998; Cunha et al., 2000). A role for endocannabinoids and $GABA_B$ receptors in this effect has also been postulated (Lourenço et al., 2010; 2011), although it contradicts data from different studies which have reported that KA effect is maintained in the presence of antagonists of these receptors (Cunha et al., 2000; Rodríguez-Moreno et al., 2000; Daw et al., 2010). Although this controversy is still not resolved, it is likely that, at least to a great extent, KA-mediated reduction in GABA release relies on the metabotropic activation of KARs. Interestingly, a KAR-dependent facilitation of GABA release has also been reported upon

activation with low concentrations of agonist (Jiang et al., 2001). Such bidirectional modulation of GABA release at low and high agonist concentrations has also been found in the supraoptic nucleus of the hypothalamus and the amygdala (Braga et al., 2003; Bonfardin et al., 2010) and seems to constitute a hallmark of KAR modulation of neurotransmitter release and plasticity (see below). Over the last years, these receptors have been shown to positively or negatively alter GABA release in a wide variety of regions, including the neocortex, the globus pallidus or the dorsal horn of the spinal cord (Ali et al., 2001; Kerchner et al., 2001; Jin and Smith, 2007).

Even though the plasticity-related consequences of such presynaptic GABA release modulation are still not clear, it has been shown that it may be result in temporal reductions of inhibitory drive over pyramidal cells upon strong excitatory input activation (Min et al., 1999). In turn, this modulation of GABA release may affect pyramidal cell output (Rodríguez-Moreno et al., 1997), adding a complexity level to the regulation of computations in circuits where KARs are present.

Regulation of neurotransmitter release during development

As we stated above, KARs expression peaks during development (Bahn et al., 1994). This temporally increased expression has been related to the modulation of important developmental processes, such as axonal growth (Tashiro et al., 2003; Marques et al., 2013), intrinsic cell excitability (Segerstråle et al., 2010) and synapse number and differentiation (Vesikansa et al., 2007; Sakha et al., 2016). Moreover, it has been repeatedly reported that KARs can control neurotransmitter release during development, further affecting circuit maturation (reviewed in Lauri and Taira, 2011). Thus, in the CA3 region, presynaptic GluK1-containing KARs differentially regulate glutamate release over pyramidal cells and interneurons. Whereas the application of the GluK1 agonist ATPA reduces mEPSC frequency in pyramidal cells, the effect is opposite in CA3 interneurons (Lauri et al., 2005). KAR action of glutamate release over CA3 cells is tonic and disappears before the second week of age. Similarly, presynaptic KARs control, in a tonic manner, the release of glutamate in a subset of CA3-CA1 synapses (Lauri et al., 2006). Again, the tonic effect is lost in juvenile animals and, whereas

KAR activation still controls glutamate release in these synapses in the adulthood (see above), the mechanism appears to be different. While both pertussis toxin and bisindolylmaleimide block KARs effect in development, pointing to a classic metabotropic action of KARs involving the activation of G_o and PKC (Sallert et al., 2007) the effect in the adulthood is only sensitive to G_o blockers, suggesting a functional interaction of this G-protein with presynaptic Ca^{2+} channels (Frerking et al., 2001). Even though the maturation mechanism involved in the loss of these tonic effects of KAR activation is not known, it has been suggested that the increases in network activity that naturally occur at the end of development may play an important role in this process (Lauri et al., 2006). Interestingly, LTP induction can conceal developmental KAR effects, and a switch in the expression of specific splice variants of GluK1 takes place at the time by which KARs effect is lost (Vesikansa et al., 2012).

As in the case of glutamate, the control of GABA release by KARs during development has also been described. In the CA1 region, ATPA depresses the amplitude of eIPSCs over pyramidal neurons, an effect independent of the activation of $GABA_B$ receptors (Maingret et al., 2005). Furthermore, KARs regulate the release of GABA from MF. It has been reported that these synapses co-release GABA during development (Beltrán and Gutiérrez, 2012; reviewed in Münster-Wandowski et al., 2013), and KARs tonically block postsynaptic currents caused by MF GABA release in a metabotropic-dependent manner (Caiati et al., 2010).

KAINATE RECEPTORS REGULATE LONG-TERM PLASTICITY

While STP processes are well suited to provide dynamic responses to transient requirements of circuit function, long-term synaptic plasticity –in the form of long-term potentiation (LTP) or depression (LTD)- are considered a physiological substrate for learning and memory (reviewed in Malenka and Bear, 2004). A wide variety of LTP and LTD processes and mechanism are now known, involving multiple mechanisms within the presynaptic, postsynaptic and glial compartments of the synapse. As in the case of STP, the participation of KARs in such LTP and

LTD processes has been repeatedly reported and, again, important controversies preclude obtaining strong conclusions in some cases.

In the hippocampus, the first instance of a role of KAR in LTP processes was described in the MF, where a novel inhibitor of the GluK1 subunit was shown to block the presynaptic form of LTP characteristic of these synapses (Bortolotto et al., 1999). This result was later confirmed by different reports (Lauri et al., 2001a; Dargan et al., 2009), and it has been shown that MF-CA3 LTP may require the activation of Ca^{2+}-permeable KARs, which in turn would activate Ca^{2+}-induced Ca^{2+} release (Lauri et al., 2003). As in the case of the involvement of GluK1 in MF-CA3 STP, evidence from different laboratories contradicts these pharmacological results, as GluK1$^{-/-}$ mice presented unaltered LTP in these synapses (Contractor et al., 2001). Furthermore, a different study was unable to replicate the pharmacological evidence described above in favor of GluK1 involvement in MF-CA3 LTP (Breustedt and Schmitz, 2004). The involvement of GluK3, but not GluK5, has also been proposed (Contractor et al., 2003; Pinheiro et al., 2007). The discrepancy between pharmacological and KO data is still maintained, although it has been postulated that the participation of GluK1 may depend on the orientation of the hippocampal slices. Thus, MF-CA3 LTP would depend on GluK1 in parasagittal but not transversal slices (Sherwood et al., 2012). On the other hand, KARs have also been shown to regulate LTP in between CA3 and CA1 cells. In contrary to MF-CA3, these synapses present a postsynaptic form of LTP, mainly triggered by NMDARs (e.g. reviewed in Volianskis et al., 2015). However, it has recently been shown that postsynaptic KARs may trigger a small NMDAR-independent component of LTP in CA3-CA1 synapses. In this occasion, KARs would signal through the activation of their metabotropic pathway, promoting the membrane insertion of AMPARs (Petrovic et al., 2017).

The activation of KARs has also been shown to promote different forms of LTP out of the hippocampus. In the lateral region of the amygdala (LA), KARs have been reported to participate in a presynaptic form of LTP that takes place at thalamocortical synapses impinging in this region (Shin et al., 2010). In a different study, a role for KARs in the regulation of presynaptic LTP of cortical input to LA was also reported (Shin et al., 2013). Interestingly, such presynaptic modulation

can be abolished by nitric oxide, a phenomenon which has not been described for KARs in other parts of the brain. It has also been reported that KARs participate in the regulation of spike timing-dependent plasticity in LA (Cho et al., 2012). Apart from the amygdala, KARs may also modulate LTP in the anterior cingulate cortex, in this case through the participation of GluK1 but not GluK2 (Koga et al., 2015).

As in the case of LTP, the participation of KARs in LTD has been widely reported. In the hippocampal CA1 region, KARs participate in a form of homosynaptic LTD induced by low frequency activation of entorhinal inputs, which impinge onto the distal region of the CA1 pyramidal cells somato-dendritic axis (Wöhrl et al., 2007). Another form of presynaptic, KAR-mediated, form of LTD has been described in the cerebellum, where parallel fiber (PF) synapses onto Purkinje cells (PC) can undergo synaptic depression upon repetitive low frequency stimulation. Intriguingly, GluK2 was found to be required for PF-PC LTD when PF stimulation was paired to PC depolarization, but not when PF stimulation was paired to climbing fiber stimulation (Crépel, 2009), although the functional relevance of this difference is still not clear. Interestingly, a role of KARs in the regulation of their own contribution to postsynaptic currents has also been described in that repetitive activation of KARs can lead to a rundown of their currents, caused by the activation of the metabotropic pathway (Rivera et al., 2007). This form of KAR LTD is complemented by a KAR-dependent mechanism of KAR internalization, which is also activated by repetitive receptor activation and involves the interaction between the GluK5 subunit and the synaptosomal protein SNAP25 (Selak et al., 2009). Finally, a different activity-dependent form of KAR LTD has been shown in the layer II-III of the perirhinal cortex, in this case through the activation of the ionotropic pathway of these receptors (Park et al., 2006). Altogether, KARs have been shown to participate in potentiation and depression processes involving a wide variety of mechanisms in the pre- and postsynaptic compartments.

CONCLUSION

Synaptic plasticity constitutes one of the crucial dynamic processes providing flexibility in neuronal inputs and outputs. Such plasticity, which takes place through an impressive variety of mechanisms, is mainly mediated by the regulation of transmitter release and its postsynaptic responses, and provides with a level of complexity that enables brain circuits to provide meaningful outputs to the ever-changing environmental conditions. Within the multiple regulators of synaptic plasticity, KARs stand out because of the outstanding characteristics of their biology. In contrast to other iGluRs, which are predominantly present in the postsynaptic compartment and signal through the ionotropic pathway (see

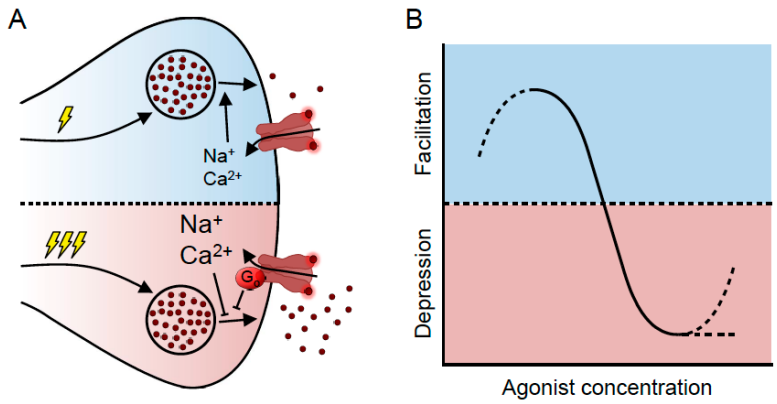

Fig 1. **Bidirectional modulation capabilities of KARs.**
(A) Presynaptic KARs can modulate transmitter release in a bidirectional manner as a function of the intensity of previous synaptic activation. Upon light synaptic activation, ionotropic activation of presynaptic KARs can facilitate transmitter release (top). Stronger activity regimes can induce KAR-mediated depression of transmitter release either by the metabotropic pathway or by ionotropic overactivation (bottom). (B) Schematic representation of the bimodal effect of presynaptic KARs upon agonist binding. Whereas low agonist concentrations facilitate transmitter release, higher concentrations depress it. The overall effect is an homeostatic maintenance of transmitter release and plasticity.

Valbuena and Lerma, 2016 for a review), the subcellular location of KARs is often presynaptic (Darstein et al., 2003), whereas their canonical and non-canonical signaling capacities are more balanced (Rodríguez-Moreno et al., 2000; Bonfardin et al., 2010). These two factors allow presynaptic KARs to modulate transmitter release –and, therefore, plasticity- in a wide variety of synapses, brain regions and developmental stages, while postsynaptic KARs can, in some occasions, regulate synaptic strength at the long term (Selak et al., 2009; Petrovic et al., 2017).

Given the extreme complexity of the presynaptic compartment and the specialized machinery dedicated to the regulation of transmitter release, the obvious question arises as to why a neurotransmitter receptor is required to further modulate this process. A plausible answer is that presynaptic receptors,

especially those acting in an homosynaptic manner, may constitute a reliable and autonomous mechanism for online measurement of transmitter release. On the other hand, heterosynaptic modulation of release through presynaptic receptors provides with a mechanism by which a given neurotransmitter system can alter signaling of a different one. Multiple examples of receptors providing such modulation have been described over decades (e.g. reviewed in Miller, 1998; Schicker et al., 2008). In the case of KARs, it has been shown that they can either promote or reduce glutamate and GABA release in different synapses and, interestingly, such modulation is bidirectional in a specific subset of them (Contractor et al., 2003; Bonfardin et al., 2010). This fact raises interesting questions about the function of this bidirectional modulation. Thus, it has been shown that low concentrations of KARs agonists, acting through their ionotropic mechanism –either by depolarizing the presynaptic terminal or by directly permeating Ca^{2+}-, can promote glutamate release from MF synapses (Schmitz et al., 2001b; Contractor et al., 2003). The consequences of this increase in glutamate release at the level of STP are pivotal, as MF-CA3 synapses of GluK2$^{-/-}$ and GluK3$^{-/-}$ mice present impaired PPF and FF (Contractor et al., 2001; Pinheiro et al., 2007) On the other hand, in the same synapses strong KAR activation leads to a reduction in the release of glutamate (Vignes et al., 1998; Bortolotto et al., 1999; Kamiya and Ozawa, 2000), likely through an excessive depolarization of the synaptic terminal (Schmitz et al., 2000). A similar bidirectional mechanism operates at different inhibitory synapses, although here the depressive effect of intense KAR activation takes place through the activation of the metabotropic pathway (Rodríguez-Moreno and Lerma, 1998; Cunha et al., 2000). Given these data, it is tempting to speculate that, under low levels of activity, KARs would facilitate neurotransmitter release, positively affecting STP. Under strong input to the presynaptic site, in contrast, KARs may negatively affect transmitter release and STP. The combination of these regulatory capacities endows KARs to act as conditional or homeostatic gatekeepers of transmitter release and STP in the synapses where they are present (Fig. 1). Future experiments may be designed in order to shed light onto this possibility. First, an undoubtful determination of the involvement of KARs and their subunits in the regulation of transmitter release and plasticity at particular synapses is absolutely required (Lauri et al., 2001b; Contractor et al., 2003; Kwon and Castillo, 2008;

Fernandes et al., 2009). Then, it would be interesting to evaluate the functional consequences of the abolishment of either the facilitatory or the inhibitory actions of KARs. This goal may be accomplished by developing approaches specifically ablating ionotropic and metabotropic actions of the receptor (in synapses where these pathways underlie opposing KAR effects) or by shifting receptor activation from light to strong or vice-versa (in synapses where only ionotropic mechanisms account for both facilitation and depression effects). Assessing the synaptic, circuit and behavioral consequences of such interventional approaches would shed light onto the interplay between ionotropic and metabotropic signaling pathways and their associated increases and decreases in synaptic gain. The importance of such gain modulations has been repeatedly reported, and may play important roles in the pathological states, such autism-spectrum disorders and Down syndrome or intellectual disability (Lanore et al., 2012; Aller et al., 2015; Arora et al., 2018; Valbuena et al., 2019). Finally, given that most of the descriptions of KARs roles in the regulation of transmitter release and synaptic plasticity derive from work in the hippocampus, it would be interesting to further explore the participation of these receptors in plasticity processes in other brain regions.

Since their discovery and along their problematic characterization, KARs have become a form of “outsider” subfamily of iGluRs. The complexity of their biology, especially regarding their signaling capacities and subcellular location, makes them capable of fine tuning a wide variety of processes. Within them, there is a growing perception regarding the important participation of KARs in the regulation of transmitter release and, subsequently, synaptic plasticity. The ability of these receptors to bidirectionally modulate these processes makes them ideal candidates to act as synaptic buffers, positively or negatively modulating plasticity depending on the short-term functional history of the synapse. We are only beginning to understand the functional consequences that this modulation may have at the level of circuit computations and brain dysfunction, pivotal points that must be evaluated in order to definitely understand these enigmatic receptors.

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REFERENCES

Ali, A.B., Rossier, J., Staiger, J.F., and Audinat, E. (2001). Kainate receptors regulate unitary IPSCs elicited in pyramidal cells by fast-spiking interneurons in the neocortex. The Journal of neuroscience : the official journal of the Society for Neuroscience *21*, 2992-2999.

Aller, M.I., Pecoraro, V., Paternain, A.V., Canals, S., and Lerma, J. (2015). Increased Dosage of High-Affinity Kainate Receptor Gene grik4 Alters Synaptic Transmission and Reproduces Autism Spectrum Disorders Features. J Neurosci *35*, 13619-13628 DOI: 10.1523/JNEUROSCI.2217-15.2015.

Arora, V., Pecoraro, V., Aller, M.I., Roman, C., Paternain, A.V., and Lerma, J. (2018). Increased Grik4 Gene Dosage Causes Imbalanced Circuit Output and Human Disease-Related Behaviors. Cell Rep *23*, 3827-3838 DOI: 10.1016/j.celrep.2018.05.086.

Bahn, S., Volk, B., and Wisden, W. (1994). Kainate receptor gene expression in the developing rat brain. Journal of Neuroscience *14*, 5525-5547 DOI: 10.1523/JNEUROSCI.14-09-05525.1994.

Beltrán, J.Q., and Gutiérrez, R. (2012). Co-release of glutamate and GABA from single, identified mossy fibre giant boutons. The Journal of Physiology *590*, 4789-4800 DOI: 10.1113/jphysiol.2012.236372.

Bonfardin, V.D., Fossat, P., Theodosis, D.T., and Oliet, S.H. (2010). Glia-dependent switch of kainate receptor presynaptic action. J Neurosci *30*, 985-995 DOI: 10.1523/JNEUROSCI.3389-09.2010.

Bortolotto, Z.A., Clarke, V.R.J., Delany, C.M., Parry, M.C., Smolders, I., Vignes, M., Ho, K.H., Miu, P., Brinton, B.T., Fantaske, R.*, et al.* (1999). Kainate receptors are involved in synaptic plasticity. Nature *402*, 297 DOI: 10.1038/46290.

Braga, M.F.M., Aroniadou-Anderjaska, V., Xie, J., and Li, H. (2003). Bidirectional Modulation of GABA Release by Presynaptic Glutamate Receptor 5 Kainate Receptors in the Basolateral Amygdala. Journal of Neuroscience *23*, 442-452 DOI: 10.1523/JNEUROSCI.23-02-00442.2003.

Breustedt, J., and Schmitz, D. (2004). Assessing the Role of GLUK5 and GLUK6 at Hippocampal Mossy Fiber Synapses. The Journal of Neuroscience *24*, 10093-10098 DOI: 10.1523/JNEUROSCI.3078-04.2004.

Bureau, I., Bischoff, S., Heinemann, S.F., and Mulle, C. (1999). Kainate Receptor-Mediated Responses in the CA1 Field of Wild-Type and GluR6-Deficient Mice. Journal of Neuroscience *19*, 653-663 DOI: 10.1523/JNEUROSCI.19-02-00653.1999.

Caiati, M.D., Sivakumaran, S., and Cherubini, E. (2010). In the developing rat hippocampus, endogenous activation of presynaptic kainate receptors reduces GABA release from mossy fiber terminals. J Neurosci *30*, 1750-1759 DOI: 10.1523/JNEUROSCI.4566-09.2010.

Castillo, P.E., Malenka, R.C., and Nicoll, R.A. (1997). Kainate receptors mediate a slow postsynaptic current in hippocampal CA3 neurons. Nature *388*, 40645 DOI: 10.1038/40645.

Contractor, A., Sailer, A.W., Darstein, M., Maron, C., Xu, J., Swanson, G.T., and Heinemann, S.F. (2003). Loss of kainate receptor-mediated heterosynaptic facilitation of mossy-fiber synapses in KA2-/- mice. The Journal of neuroscience : the official journal of the Society for Neuroscience *23*, 422-429.

Contractor, A., Swanson, G., and Heinemann, S.F. (2001). Kainate Receptors Are Involved in Short- and Long-Term Plasticity at Mossy Fiber Synapses in the Hippocampus. Neuron *29*, 209-216 DOI: 10.1016/S0896-6273(01)00191-X.

Contractor, A., Swanson, G.T., Sailer, A., O'Gorman, S., and Heinemann, S.F. (2000). Identification of the kainate receptor subunits underlying modulation of excitatory synaptic transmission in the CA3 region of the hippocampus. The Journal of neuroscience : the official journal of the Society for Neuroscience *20*, 8269-8278.

Cossart, R., Esclapez, M., Hirsch, J.C., Bernard, C., and Ben-Ari, Y. (1998). GluR5 kainate receptor activation in interneurons increases tonic inhibition of pyramidal cells. Nature Neuroscience *1* DOI: 10.1038/2185.

Crépel, F. (2009). Role of Presynaptic Kainate Receptors at Parallel Fiber–Purkinje Cell Synapses in Induction of Cerebellar LTD: Interplay With Climbing Fiber Input. Journal of Neurophysiology *102*, 965-973 DOI: 10.1152/jn.00269.2009.

Cunha, R.A., Constantino, M.D., and Ribeiro, J.A. (1997). Inhibition of [3H] gamma-aminobutyric acid release by kainate receptor activation in rat

hippocampal synaptosomes. European journal of pharmacology *323*, 167-172 DOI: 10.1016/s0014-2999(97)00043-5.

Cunha, R.A., Malva, J.O., and Ribeiro, J.A. (1999). Kainate receptors coupled to G(i)/G(o) proteins in the rat hippocampus. Molecular pharmacology *56*, 429-433.

Cunha, R.A., Malva, J.O., and Ribeiro, J.A. (2000). Pertussis toxin prevents presynaptic inhibition by kainate receptors of rat hippocampal [3H]GABA release. FEBS Letters *469*, 159-162 DOI: 10.1016/S0014-5793(00)01272-2.

Curtis, D.R., and Watkins, J.C. (1960). THE EXCITATION AND DEPRESSION OF SPINAL NEURONES BY STRUCTURALLY RELATED AMINO ACIDS. Journal of Neurochemistry *6*, 117-141 DOI: 10.1111/j.1471-4159.1960.tb13458.x.

Chittajallu, R., Vignes, M., Dev, K.K., Barnes, J.M., Collingridge, G.L., and Henley, J.M. (1996). Regulation of glutamate release by presynaptic kainate receptors in the hippocampus. Nature *379*, 78-81 DOI: 10.1038/379078a0.

Cho, J.-H., Bayazitov, I.T., Meloni, E.G., Myers, K.M., Jr, W.A., Zakharenko, S.S., and Bolshakov, V.Y. (2012). Coactivation of thalamic and cortical pathways induces input timing–dependent plasticity in amygdala. Nature Neuroscience *15*, 113 DOI: 10.1038/nn.2993.

Christensen, J.K., Paternain, A.V., Selak, S., Ahring, P.K., and Lerma, J. (2004). A Mosaic of Functional Kainate Receptors in Hippocampal Interneurons. The Journal of Neuroscience *24*, 8986-8993 DOI: 10.1523/JNEUROSCI.2156-04.2004.

Dargan, S.L., Clarke, V., Alushin, G.M., Sherwood, J.L., Nisticò, R., Bortolotto, Z.A., Ogden, A.M., Bleakman, D., Doherty, A.J., Lodge, D.*, et al.* (2009). ACET is a highly potent and specific kainate receptor antagonist: Characterisation and effects on hippocampal mossy fibre function. Neuropharmacology *56*, 121-130 DOI: 10.1016/j.neuropharm.2008.08.016.

Darstein, M., Petralia, R.S., Swanson, G.T., Wenthold, R.J., and Heinemann, S.F. (2003). Distribution of Kainate Receptor Subunits at Hippocampal Mossy Fiber Synapses. Journal of Neuroscience *23*, 8013-8019 DOI: 10.1523/JNEUROSCI.23-22-08013.2003.

Daw, M.I., Pelkey, K.A., Chittajallu, R., and McBain, C.J. (2010). Presynaptic Kainate Receptor Activation Preserves Asynchronous GABA Release Despite the Reduction in Synchronous Release from Hippocampal Cholecystokinin Interneurons. The Journal of Neuroscience *30*, 11202-11209 DOI: 10.1523/JNEUROSCI.6334-09.2010.

Dubois, C.J., Lachamp, P.M., Sun, L., Mishina, M., and Liu, S. (2016). Presynaptic GluN2D receptors detect glutamate spillover and regulate cerebellar GABA release. Journal of Neurophysiology *115*, 271-285 DOI: 10.1152/jn.00687.2015.

Fernandes, H.B., Catches, J.S., Petralia, R.S., Copits, B.A., Xu, J., Russell, T.A., Swanson, G.T., and Contractor, A. (2009). High-Affinity Kainate Receptor Subunits Are Necessary for Ionotropic but Not Metabotropic Signaling. Neuron *63*, 818-829 DOI: 10.1016/j.neuron.2009.08.010.

Frerking, M., Malenka, R.C., and Nicoll, R.A. (1998). Synaptic activation of kainate receptors on hippocampal interneurons. Nature neuroscience *1*, 479-486 DOI: 10.1038/2194.

Frerking, M., and Ohliger-Frerking, P. (2002). AMPA Receptors and Kainate Receptors Encode Different Features of Afferent Activity. Journal of Neuroscience *22*, 7434-7443 DOI: 10.1523/JNEUROSCI.22-17-07434.2002.

Frerking, M., Schmitz, D., Zhou, Q., Johansen, J., and Nicoll, R.A. (2001). Kainate Receptors Depress Excitatory Synaptic Transmission at CA3→CA1 Synapses in the Hippocampus via a Direct Presynaptic Action. Journal of Neuroscience *21*, 2958-2966 DOI: 10.1523/JNEUROSCI.21-09-02958.2001.

Goldin, M., Epsztein, J., Jorquera, I., Represa, A., Ben-Ari, Y., Crepel, V., and Cossart, R. (2007). Synaptic kainate receptors tune oriens-lacunosum moleculare interneurons to operate at theta frequency. J Neurosci *27*, 9560-9572 DOI: 10.1523/JNEUROSCI.1237-07.2007.

Hayashi, T. (1954). EFFECTS OF SODIUM GLUTAMATE ON THE NERVOUS SYSTEM. The Keio Journal of Medicine *3*, 183-192 DOI: 10.2302/kjm.3.183.

Henze, D.A., Wittner, L., and Buzsáki, G. (2002). Single granule cells reliably discharge targets in the hippocampal CA3 network in vivo. Nature Neuroscience *5* DOI: 10.1038/nn887.

Jiang, L., Xu, J., Nedergaard, M., and Kang, J. (2001). A Kainate Receptor Increases the Efficacy of GABAergic Synapses. Neuron *30*, 503-513 DOI: 10.1016/S0896-6273(01)00298-7.

Jin, X.T., and Smith, Y. (2007). Activation of presynaptic kainate receptors suppresses GABAergic synaptic transmission in the rat globus pallidus. Neuroscience *149*, 338-349 DOI: 10.1016/j.neuroscience.2007.07.017.

Kamiya, H., and Ozawa, S. (1998). Kainate receptor-mediated inhibition of presynaptic Ca2+ influx and EPSP in area CA1 of the rat hippocampus. The Journal of physiology *509 (Pt 3)*, 833-845 DOI: 10.1111/j.1469-7793.1998.833bm.x.

Kamiya, H., and Ozawa, S. (2000). Kainate receptor-mediated presynaptic inhibition at the mouse hippocampal mossy fibre synapse. The Journal of Physiology *523*, 653-665 DOI: 10.1111/j.1469-7793.2000.t01-1-00653.x.

Kerchner, G.A., Wang, G.-D., Qiu, C.-S., Huettner, J.E., and Zhuo, M. (2001). Direct Presynaptic Regulation of GABA/Glycine Release by Kainate Receptors in the Dorsal Horn An Ionotropic Mechanism. Neuron *32*, 477-488 DOI: 10.1016/S0896-6273(01)00479-2.

Koga, K., Descalzi, G., Chen, T., Ko, H.-G., Lu, J., Li, S., Son, J., Kim, T., Kwak, C., Huganir, R.L.*, et al.* (2015). Coexistence of Two Forms of LTP in ACC Provides a Synaptic Mechanism for the Interactions between Anxiety and Chronic Pain. Neuron *85*, 377-389 DOI: 10.1016/j.neuron.2014.12.021.

Krogsgaard-Larsen, P., Honoré, T., Hansen, J.J., Curtis, D.R., and Lodge, D. (1980). New class of glutamate agonist structurally related to ibotenic acid. Nature *284*, 64-66.

Kwon, H.-B., and Castillo, P.E. (2008). Role of Glutamate Autoreceptors at Hippocampal Mossy Fiber Synapses. Neuron *60*, 1082-1094 DOI: 10.1016/j.neuron.2008.10.045.

Lanore, F., Labrousse, V.F., Szabo, Z., Normand, E., Blanchet, C., and Mulle, C. (2012). Deficits in Morphofunctional Maturation of Hippocampal Mossy Fiber Synapses in a Mouse Model of Intellectual Disability. The Journal of Neuroscience *32*, 17882-17893 DOI: 10.1523/JNEUROSCI.2049-12.2012.

Lauri, S.E., Bortolotto, Z.A., Bleakman, D., Ornstein, P.L., Lodge, D., Isaac, J., and Collingridge, G.L. (2001a). A Critical Role of a Facilitatory Presynaptic Kainate Receptor in Mossy Fiber LTP. Neuron *32*, 697-709 DOI: 10.1016/S0896-6273(01)00511-6.

Lauri, S.E., Bortolotto, Z.A., Nistico, R., Bleakman, D., Ornstein, P.L., Lodge, D., Isaac, J., and Collingridge, G.L. (2003). A Role for Ca2+ Stores in Kainate Receptor-Dependent Synaptic Facilitation and LTP at Mossy Fiber Synapses in the Hippocampus. Neuron *39*, 327-341 DOI: 10.1016/S0896-6273(03)00369-6.

Lauri, S.E., Delany, C., Clarke, V.R.J., Bortolotto, Z.A., Ornstein, P.L., Isaac, J., and Collingridge, G.L. (2001b). Synaptic activation of a presynaptic kainate receptor facilitates AMPA receptor-mediated synaptic transmission at

hippocampal mossy fibre synapses. Neuropharmacology *41*, 907-915 DOI: 10.1016/S0028-3908(01)00152-6.

Lauri, S.E., Segerstråle, M., Vesikansa, A., Maingret, F., Mulle, C., Collingridge, G.L., Isaac, J.T.R., and Taira, T. (2005). Endogenous Activation of Kainate Receptors Regulates Glutamate Release and Network Activity in the Developing Hippocampus. The Journal of Neuroscience *25*, 4473-4484 DOI: 10.1523/JNEUROSCI.4050-04.2005.

Lauri, S.E., and Taira, T. (2011). Kainate Receptors, Novel Signaling Insights. Kainate Receptors, Novel Signaling Insights, 81-91 DOI: 10.1007/978-1-4419-9557-5_8.

Lauri, S.E., Vesikansa, A., Segerstråle, M., Collingridge, G.L., Isaac, J., and Taira, T. (2006). Functional Maturation of CA1 Synapses Involves Activity-Dependent Loss of Tonic Kainate Receptor-Mediated Inhibition of Glutamate Release. Neuron *50*, 415-429 DOI: 10.1016/j.neuron.2006.03.020.

Lerma J. (2011) Net(o) excitement for kainate receptors. Naure Neurosci. 14:808–810.

Lerma, J., and Marques, J.M. (2013). Kainate receptors in health and disease. Neuron *80*, 292-311 DOI: 10.1016/j.neuron.2013.09.045.

Lerma, J., Paternain, A.V., Rodríguez-Moreno, A., and López-García, J.C. (2001). Molecular physiology of kainate receptors. Physiological reviews *81*, 971-998 DOI: 10.1152/physrev.2001.81.3.971.

Lourenço, J., Cannich, A., Carta, M., Coussen, F., Mulle, C., and Marsicano, G. (2010). Synaptic activation of kainate receptors gates presynaptic CB1 signaling at GABAergic synapses. Nature Neuroscience *13*, 197 DOI: 10.1038/nn.2481.

Lourenço, J., Matias, I., Marsicano, G., and Mulle, C. (2011). Pharmacological Activation of Kainate Receptors Drives Endocannabinoid Mobilization. The Journal of Neuroscience *31*, 3243-3248 DOI: 10.1523/JNEUROSCI.3512-10.2011.

Maingret, F., Lauri, S.E., Taira, T., and Isaac, J.T.R. (2005). Profound regulation of neonatal CA1 rat hippocampal GABAergic transmission by functionally distinct kainate receptor populations. The Journal of Physiology *567*, 131-142 DOI: 10.1113/jphysiol.2005.089474.

Malenka, R.C., and Bear, M.F. (2004). LTP and LTD: an embarrassment of riches. Neuron *44*, 5-21 DOI: 10.1016/j.neuron.2004.09.012.

Marques, J.M., Rodrigues, R.J., Valbuena, S., Rozas, J.L., Selak, S., Marin, P., Aller, M.I., and Lerma, J. (2013). CRMP2 Tethers Kainate Receptor Activity to Cytoskeleton Dynamics during Neuronal Maturation. The Journal of Neuroscience *33*, 18298-18310 DOI: 10.1523/JNEUROSCI.3136-13.2013.

Melyan, Z., Lancaster, B., and Wheal, H.V. (2004). Metabotropic Regulation of Intrinsic Excitability by Synaptic Activation of Kainate Receptors. The Journal of Neuroscience *24*, 4530-4534 DOI: 10.1523/JNEUROSCI.5356-03.2004.

Miller, R.J. (1998). Presynaptic receptors. Annual review of pharmacology and toxicology *38*, 201-227 DOI: 10.1146/annurev.pharmtox.38.1.201.

Min, M.-Y., Melyan, Z., and Kullmann, D.M. (1999). Synaptically released glutamate reduces γ-aminobutyric acid (GABA)ergic inhibition in the hippocampus via kainate receptors. Proceedings of the National Academy of Sciences *96*, 9932-9937 DOI: 10.1073/pnas.96.17.9932.

Münster-Wandowski, A., Gómez-Lira, G., and Gutiérrez, R. (2013). Mixed neurotransmission in the hippocampal mossy fibers. Frontiers in cellular neuroscience *7*, 210 DOI: 10.3389/fncel.2013.00210.

Nicoll, R.A., and Schmitz, D. (2005). Synaptic plasticity at hippocampal mossy fibre synapses. Nature Reviews Neuroscience *6* DOI: 10.1038/nrn1786.

Niswender, C.M., and Conn, P.J. (2010). Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annual review of pharmacology and toxicology *50*, 295-322 DOI: 10.1146/annurev.pharmtox.011008.145533.

Palacios-Filardo, J., Aller, I.M., and Lerma, J. (2016). Synaptic Targeting of Kainate Receptors. Cerebral Cortex *26*, 1464-1472 DOI: 10.1093/cercor/bhu244.

Park, Y., Jo, J., Isaac, J., and Cho, K. (2006). Long-Term Depression of Kainate Receptor-Mediated Synaptic Transmission. Neuron *49*, 95-106 DOI: 10.1016/j.neuron.2005.11.035.

Partovi, D., and Frerking, M. (2006). Presynaptic inhibition by kainate receptors converges mechanistically with presynaptic inhibition by adenosine and GABAB receptors. Neuropharmacology *51*, 1030-1037 DOI: 10.1016/j.neuropharm.2006.06.010.

Paternain, A.V., Herrera, M.a.T., Nieto, A.M., and Lerma, J. (2000). GluR5 and GluR6 Kainate Receptor Subunits Coexist in Hippocampal Neurons and

Coassemble to Form Functional Receptors. Journal of Neuroscience *20*, 196-205 DOI: 10.1523/JNEUROSCI.20-01-00196.2000.

Petrovic, M.M., da Silva, S., Clement, J.P., Vyklicky, L., Mulle, C., González-González, I.M., and Henley, J.M. (2017). Metabotropic action of postsynaptic kainate receptors triggers hippocampal long-term potentiation. Nature Neuroscience *20*, 529-539 DOI: 10.1038/nn.4505.

Pinheiro, P.S., Perrais, D., Coussen, F., Barhanin, J., Bettler, B., Mann, J.R., Malva, J.O., Heinemann, S.F., and Mulle, C. (2007). GluR7 is an essential subunit of presynaptic kainate autoreceptors at hippocampal mossy fiber synapses. Proceedings of the National Academy of Sciences *104*, 12181-12186 DOI: 10.1073/pnas.0608891104.

Rivera, R., Rozas, J., and Lerma, J. (2007). PKC-dependent autoregulation of membrane kainate receptors. The EMBO Journal *26*, 4359-4367 DOI: 10.1038/sj.emboj.7601865.

Rodríguez-Moreno, A., Herreras, O., and Lerma, J. (1997). Kainate Receptors Presynaptically Downregulate GABAergic Inhibition in the Rat Hippocampus. Neuron *19*, 893-901 DOI: 10.1016/S0896-6273(00)80970-8.

Rodríguez-Moreno, A., and Lerma, J. (1998). Kainate Receptor Modulation of GABA Release Involves a Metabotropic Function. Neuron *20*, 1211-1218 DOI: 10.1016/S0896-6273(00)80501-2.

Rodríguez-Moreno, A., López-García, J.C., and Lerma, J. (2000). Two populations of kainate receptors with separate signaling mechanisms in hippocampal interneurons. Proceedings of the National Academy of Sciences *97*, 1293-1298 DOI: 10.1073/pnas.97.3.1293.

Rozas, J., Paternain, A.V., and Lerma, J. (2003). Noncanonical Signaling by Ionotropic Kainate Receptors. Neuron *39*, 543-553 DOI: 10.1016/S0896-6273(03)00436-7.

Rutkowska-Wlodarczyk, I., Aller, I.M., Valbuena, S., Bologna, J.-C., Prézeau, L., and Lerma, J. (2015). A Proteomic Analysis Reveals the Interaction of GluK1 Ionotropic Kainate Receptor Subunits with Go Proteins. The Journal of Neuroscience *35*, 5171-5179 DOI: 10.1523/JNEUROSCI.5059-14.2015.

Sakha, P., Vesikansa, A., Orav, E., Heikkinen, J., Kukko-Lukjanov, T.-K., Shintyapina, A., Franssila, S., Jokinen, V., Huttunen, H.J., and Lauri, S.E. (2016). Axonal Kainate Receptors Modulate the Strength of Efferent Connectivity by Regulating Presynaptic Differentiation. Frontiers in Cellular Neuroscience *10*, 3 DOI: 10.3389/fncel.2016.00003.

Sallert, M., Malkki, H., Segerstråle, M., Taira, T., and Lauri, S.E. (2007). Effects of the kainate receptor agonist ATPA on glutamatergic synaptic transmission and plasticity during early postnatal development. Neuropharmacology *52*, 1354-1365 DOI: 10.1016/j.neuropharm.2007.01.015.

Schicker, K.W., Dorostkar, M.M., and Boehm, S. (2008). Modulation of transmitter release via presynaptic ligand-gated ion channels. Current molecular pharmacology *1*, 106-129.

Schmitz, D., Frerking, M., and Nicoll, R.A. (2000). Synaptic activation of presynaptic kainate receptors on hippocampal mossy fiber synapses. Neuron *27*, 327-338 DOI: 10.1016/s0896-6273(00)00040-4.

Schmitz, D., Mellor, J., Frerking, M., and Nicoll, R.A. (2001a). Presynaptic kainate receptors at hippocampal mossy fiber synapses. Proceedings of the National Academy of Sciences *98*, 11003-11008 DOI: 10.1073/pnas.191351498.

Schmitz, D., Mellor, J., and Nicoll, R.A. (2001b). Presynaptic kainate receptor mediation of frequency facilitation at hippocampal mossy fiber synapses. Science (New York, NY) *291*, 1972-1976 DOI: 10.1126/science.1057105.

Segerstråle, M., Juuri, J., Lanore, F., Piepponen, P., Lauri, S.E., Mulle, C., and Taira, T. (2010). High Firing Rate of Neonatal Hippocampal Interneurons Is Caused by Attenuation of Afterhyperpolarizing Potassium Currents by Tonically Active Kainate Receptors. The Journal of Neuroscience *30*, 6507-6514 DOI: 10.1523/JNEUROSCI.4856-09.2010.

Selak, S., Paternain, A.V., Aller, M.I., Pico, E., Rivera, R., and Lerma, J. (2009). A role for SNAP25 in internalization of kainate receptors and synaptic plasticity. Neuron *63*, 357-371 DOI: 10.1016/j.neuron.2009.07.017.

Sherwood, J.L., Amici, M., Dargan, S.L., Culley, G.R., Fitzjohn, S.M., Jane, D.E., Collingridge, G.L., Lodge, D., and Bortolotto, Z.A. (2012). Differences in kainate receptor involvement in hippocampal mossy fibre long-term potentiation depending on slice orientation. Neurochemistry International *61*, 482-489 DOI: 10.1016/j.neuint.2012.04.021.

Shin, R.-M., Higuchi, M., and Suhara, T. (2013). Nitric Oxide Signaling Exerts Bidirectional Effects on Plasticity Inductions in Amygdala. PLoS ONE *8* DOI: 10.1371/journal.pone.0074668.

Shin, R.-M., Tully, K., Li, Y., Cho, J.-H., Higuchi, M., Suhara, T., and Bolshakov, V.Y. (2010). Hierarchical order of coexisting pre- and postsynaptic forms of long-

term potentiation at synapses in amygdala. Proceedings of the National Academy of Sciences *107*, 19073-19078 DOI: 10.1073/pnas.1009803107.

Shinozaki, H., and Shibuya, I. (1974). Potentiation of glutamate-induced depolarization by kainic acid in the crayfish opener muscle. Neuropharmacology *13*, 1057-1065 DOI: 10.1016/0028-3908(74)90096-3.

Straub, C., Hunt, D.L., Yamasaki, M., Kim, K.S., Watanabe, M., Castillo, P.E., and Tomita, S. (2011). Distinct functions of kainate receptors in the brain are determined by the auxiliary subunit Neto1. Nature Neuroscience *14*, 866 DOI: 10.1038/nn.2837.

Sylwestrak, E.L., and Ghosh, A. (2012). Elfn1 regulates target-specific release probability at CA1-interneuron synapses. Science (New York, NY) *338*, 536-540 DOI: 10.1126/science.1222482.

Takago, H., Nakamura, Y., and Takahashi, T. (2005). G protein-dependent presynaptic inhibition mediated by AMPA receptors at the calyx of Held. Proceedings of the National Academy of Sciences of the United States of America *102*, 7368-7373 DOI: 10.1073/pnas.0408514102.

Tashiro, A., Dunaevsky, A., Blazeski, R., Mason, C.A., and Yuste, R. (2003). Bidirectional Regulation of Hippocampal Mossy Fiber Filopodial Motility by Kainate Receptors A Two-Step Model of Synaptogenesis. Neuron *38*, 773-784 DOI: 10.1016/S0896-6273(03)00299-X.

Traynelis, S.F., Wollmuth, L.P., McBain, C.J., Menniti, F.S., Vance, K.M., Ogden, K.K., Hansen, K.B., Yuan, H., Myers, S.J., and Dingledine, R. (2010). Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev *62*, 405-496 DOI: 10.1124/pr.109.002451.

Valbuena, S., and Lerma, J. (2016). Non-canonical Signaling, the Hidden Life of Ligand-Gated Ion Channels. Neuron *92*, 316-329 DOI: 10.1016/j.neuron.2016.10.016.

Valbuena, S., García, A., Mazier, W., Paternain, A.V., and Lerma, J. (2019). Unbalanced dendritic inhibition of CA1 neurons drives spatial-memory deficits in the Ts2Cje Down syndrome model. Nature Communications, *10*, 4991-12. DOI:10.1038/s41467-019-13004-9.

Vesikansa, A., Sakha, P., Kuja-Panula, J., Molchanova, S., Rivera, C., Huttunen, H.J., Rauvala, H., Taira, T., and Lauri, S.E. (2012). Expression of GluK1c underlies the developmental switch in presynaptic kainate receptor function. Scientific Reports *2*, 310 DOI: 10.1038/srep00310.

Vesikansa, A., Sallert, M., Taira, T., and Lauri, S.E. (2007). Activation of kainate receptors controls the number of functional glutamatergic synapses in the area CA1 of rat hippocampus. The Journal of Physiology *583*, 145-157 DOI: 10.1113/jphysiol.2007.133975.

Vignes, M., Clarke, V.R.J., Parry, M.J., Bleakman, D., Lodge, D., Ornstein, P.L., and Collingridge, G.L. (1998). The GluR5 subtype of kainate receptor regulates excitatory synaptic transmission in areas CA1 and CA3 of the rat hippocampus. Neuropharmacology *37*, 1269-1277 DOI: 10.1016/S0028-3908(98)00148-8.

Vignes, M., and Collingridge, G.L. (1997). The synaptic activation of kainate receptors. Nature *388*, 179-182 DOI: 10.1038/40639.

Volianskis, A., France, G., Jensen, M.S., Bortolotto, Z.A., Jane, D.E., and Collingridge, G.L. (2015). Long-term potentiation and the role of N-methyl-d-aspartate receptors. Brain Research *1621*, 5-16 DOI: 10.1016/j.brainres.2015.01.016.

Wöhrl, R., Haebler, D., and Heinemann, U. (2007). Low-frequency stimulation of the direct cortical input to area CA1 induces homosynaptic LTD and heterosynaptic LTP in the rat hippocampal–entorhinal cortex slice preparation. European Journal of Neuroscience *25*, 251-258 DOI: 10.1111/j.1460-9568.2006.05274.x.

Wyeth, M.S., Pelkey, K.A., Yuan, X., Vargish, G., Johnston, A.D., Hunt, S., Fang, C., Abebe, D., Mahadevan, V., Fisahn, A.*, et al.* (2017). Neto Auxiliary Subunits Regulate Interneuron Somatodendritic and Presynaptic Kainate Receptors to Control Network Inhibition. Cell Reports *20*, 2156-2168 DOI: 10.1016/j.celrep.2017.08.017.

Zhang, W., St-Gelais, F., Grabner, C.P., Trinidad, J.C., Sumioka, A., Morimoto-Tomita, M., Kim, K.S., Straub, C., Burlingame, A.L., Howe, J.R.*, et al.* (2009). A Transmembrane Accessory Subunit that Modulates Kainate-Type Glutamate Receptors. Neuron *61*, 385-396 DOI: 10.1016/j.neuron.2008.12.014.

Ziegra, C.J., Willard, J.M., and Oswald, R.E. (1992). Coupling of a purified goldfish brain kainate receptor with a pertussis toxin-sensitive G protein. Proceedings of the National Academy of Sciences *89*, 4134-4138 DOI: 10.1073/pnas.89.9.4134.