Chapter

Kainate Receptors Modulating Glutamate Release in the Cerebellum

Pilar Losada-Ruiz, Rafael Falcón-Moya and Antonio Rodríguez-Moreno

Abstract

Glutamate receptors of the kainate type (Kainate receptors, KARs), are mediators of ionotropic postsynaptic synaptic transmission, as well as presynaptic modulators of neurotransmitter release where they show both ionotropic and metabotropic actions regulating glutamate and γ-aminobutiric acid (GABA) release. The mechanisms underlying these modulatory roles are starting to be understood at some brain regions. Here we review the KARs roles and mechanisms involved in the modulation of glutamate release in the cerebellum at parallel fibers (PF)-Purkinje Cells (PuC) synapses. KARs activation mediate a biphasic effect on glutamate release at this synapse, with low kainate (KA) concentrations mediating a facilitation of glutamate release and higher KA concentrations mediating a depression of glutamate release. KA-mediated facilitation is prevented by antagonizing KARs, by inhibition of PKA or stimulation of adenylyl cyclase (AC), by blocking Ca^{2+} permeant KARs, by depleting intracellular Ca^{2+} stores and by blocking calmodulin. Thus, at cerebellar parallel fiber-Purkinje cell synapses, presynaptic KARs mediate glutamate release facilitation through Ca^{2+}-calmodulin dependent activation of adenylyl cyclase/cAMP/protein kinase A signaling. KAR-mediated depression of glutamate release involves the AC/cAMP/PKA pathway as for facilitation but not Ca^{2+}-calmodulin, being in this case AC activated by a Gi/o protein to mediate a depression of glutamate release.

Keywords: cerebellum, KARs, glutamate release, presynaptic, PKA, adenylate cyclase, Ca^{2+} calmodulin

1. Introduction

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system (CNS) of mammals. Glutamate mediates its actions by activating glutamate receptors. These receptors participate in normal synaptic transmission at different synapses, in plasticity processes as long-term potentiation (LTP) and long-term depression (LTD) that are considered the cellular and molecular correlation of memory and learning processes and in synaptogenesis and neuronal maturation and, additionally, failure in the functioning of this system can be the origin of some types of epilepsy and may contribute to the development of CNS disorders such as

Alzheimer's disease, Huntington's Korea, amyotrophic lateral sclerosis, Parkinson's disease, hypoglycemia, or cerebral ischemia [1–3].

Glutamate receptors are classically divided into two large families: ionotropic and metabotropic. Ionotropic glutamate receptors (iGluRs) participate in rapid neurotransmission in the nervous system; these ionotropic receptors are classified into three types depending on the agonist that activates them with higher affinity: N-methyl-D-aspartic acid (NMDA) receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs), and kainate receptors (KARs). These receptors form a channel with different selectivity depending on their subunit composition, all of them being permeable to Na^+ and K^+ and, additionally, NMDARs are permeable to Ca^{2+} been some AMPARs and KARs also permeable to Ca^{2+} depending on subunit composition. They are integral membrane proteins, formed by four subunits (tetramers), being homomers or heteromers [1, 2].

Metabotropic glutamate receptors (mGluRs), which participate also in neurotransmission, are coupled to G proteins and are divided into eight types (mGluR 1–8) and three groups of receptors: group I mGluRs includes mGluR1 and mGluR5 receptors. These receptors are positively coupled to phospholipase C (PLC), which facilitates the conversion of inositol diphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3). DAG activates protein kinase C (PKC) that phosphorylates different substrates and IP3 causes numerous intracellular effects, including the facilitation of Ca^{2+} release from intracellular stores. Group II mGluRs includes mGluR2 and mGluR3 receptors. These receptors are negatively coupled to adenylate cyclase-mediated AMPc formation, and group III mGluRs includes mGluR4, mGluR6, mGluR7, and mGluR8 receptors. These receptors are negatively coupled to the formation of AMPc mediated by adenylate cyclase [4].

1.1 Kainate receptors

Kainate (KA) is a potent neurotoxin derived from the alga *Digenea simplex*. The word "Kainic" is derived from the Japanese "Kaininso" ("Makuri"), which means "the ghost of the sea," and it is an agonist for both KARs and AMPARs (in the same way that the AMPARs agonist AMPA may activate KARs). Kainate is classically known for its potent epileptogenic actions [5, 6].

KA (and other agonists) activates KARs that are tetramers that resulted from different combinations of five subunits called GluK1, GluK2, GluK3, GluK4, and GluK5 (formerly known as GluR5, GluR6, GluR7 and KA1, and KA2, respectively). Of these subunits, GluK1 and GluK3 may form homomeric or heteromeric functional receptors, while GluK4 and GluK5 may only participate in functional receptors when associated with any of the GluK1, GluK2, or GluK3 subunits, but they do not combine with subunits of AMPARs [1, 7, 8].

KARs have been described in different invertebrates such as nematodes and flies [9, 10] and in different species of vertebrates such as amphibia, fish, and birds [11–13] in addition to mammals. In mammals, KARs have been observed virtually throughout the entire nervous system, although their subcellular location has not been yet fully determined. KARs are widely distributed throughout the CNS and found in the main cells and interneurons of the hippocampus, lateral amygdala, dorsal root ganglia, bipolar cells of the retina, cerebral cortex, and the cerebellum [14, 15].

The lack of knowledge about these receptors compared to other glutamatergic receptors (AMPARs or NMDARs) has been due to the lack of good agonist and

antagonist for receptors with particular subunit compositions and to the absence of specific antibodies for the different subunits of KARs, being therefore a significant limitation when exploring the distribution of these receptors. However, by using in situ hybridization techniques, it has been observed that the cells that present a significant expression of the kainate-type subunits GluK1, GluK2, GluK3, and GluK5 are distributed throughout the CNS, including nucleus striatum, hippocampus, cortex, and cerebellum [16]. Likewise, there is a high expression of the GluK4 subunit in the CA3 region of the hippocampus, as well as in the granular neurons of the dentate gyrus. The messenger of the GluK5 subunit, on the other hand, appears more abundantly and more extensively than that of the GluK4 subunit or those of the other subunits [15]. Because the in situ hybridization technique is informative and cannot reveal the subcellular distribution of a specific subunit, and because of pharmacological limitations, there is still much to know about the subcellular location and physiology of these receptors.

Kainate-type glutamate receptors are well established mediators of canonical, ionotropic postsynaptic synaptic transmission and, presynaptically, have a modulatory role in regulating neurotransmitter release. In the latter regard, KARs have been shown to have a noncanonical metabotropic capacity, whereby they affect the control of both glutamate and GABA release, for review see [15, 17–22]. At some excitatory glutamatergic synapses, KARs' activation can actually effect biphasic modulation, where low agonist concentrations facilitate glutamate release, while high concentrations decrease the release of the neurotransmitter, for review see [17, 18]. Mechanistic details of how this is achieved are subject of investigation and, indeed, the subcellular location of KARs responsible for presynaptic modulation remains contentious. Different roles of KARs in plasticity have also been described either in LTP or LTD, see [23] for a review of the role of KARs in plasticity.

As other glutamate receptors, KARs are directly or indirectly involved in different diseases, alterations of the nervous system and neurodegeneration and cell death processes. As previously indicated, KA is a potent neurotoxin that directly induces epilepsy and is used as a temporal lobe epilepsy model [5, 6]. Several lines of research indicate that KA directly activating KARs is involved in excitatory and inhibitory imbalances associated with epilepsy. The use of animal models for epilepsy through the use of KA injections has allowed to reproduce in great detail the symptoms observed in humans. The majority of studies of KARs' involvement in epilepsy have studied acute KA-induced seizures [24–27]. The best demonstrations of a mechanism for KARs' involvement in acute epilepsy come from studies of inhibition of GABA release by the activation of presynaptic KA receptors at interneuron-CA1 hippocampal synapses [24, 28, 29]. In chronic epilepsy, a role of KARs has been demonstrated at hippocampal mossy fibers making aberrant synapses onto granule cells of dentate gyrus expressing high number of KARs [30–32] reviewed in [6, 33]. In humans, genetic studies of members of a family affected by idiopathic juvenile absence epilepsy found elevated levels of Grik1 polymorphisms [34], and in TLE patients, GluK1 subunit containing KARs' increased levels have also been found [35]. In clinical studies, NS1209 (an AMPA/KARs' antagonist) has been found to decrease epileptic symptoms [36].

Different studies of neurotoxicity clearly indicate that KARs might be important targets for neuroprotection in neurons and glial cells. The mechanism by which KARs produce excitotoxicity and neuronal cell death is not well understood mainly because of the limitations in appropriate pharmacological tools. Toxicity of KARs involved in multiple sclerosis has also been found onto oligodendrocytes and myelin related to [37, 38], and damage has also been found at axonal levels, where AMPA/KARs' antagonists prevent it [39]. Interestingly, KARs have also been

involved in pain. They are present at dorsal roots activating nociceptors, actually there are clinical trials using KARs' antagonists to try to prevent pain showing some levels of analgesia [36]. Additionally, KARs have been involved in ischemia [40, 41], migraine pain [36], Alzheimer's disease [42], Parkinson's disease [43, 44], Huntington's Chorea [45–47], Schizophrenia [48, 49], depression [50], bipolar disorder [51, 52], mental retardation [53], and autism [54, 55] as reviewed in [56]. In general, antagonists of KARs containing particular subunits might be good targets to ameliorate symptoms or treat different CNS diseases and alterations.

2. KARs in the cerebellum

As indicated above, KARs are expressed in the cerebellar cortex [57–59]. As known, the cerebellum participates in the modulation of movement by modifying the activity patterns of motor neurons. Structurally, the cerebellum is composed of the laminar cerebellar cortex and the deep cerebellar nuclei and has five types of cells: Purkinje, stellate, basket, Golgi, and granule cells. Purkinje cells (PuC) are aligned in front of each other. Their dendritic trees form two 2-dimensional layers through which parallel fibers from the mossy fibers located in the granular layer pass. These parallel fibers (PF) establish excitatory synapses between granular cells and the spines of the PCs dendrites as well as the climbing fibers (CF, originating from the inferior olivary nucleus) with the nearby dendrites and the cellular soma. The parallel fibers pass orthogonally through the dendritic tree of the Purkinje neuron. Up to 200,000 PF form a synapse with a single PuC. Each PuC receives up to 500 synapses of CF, all originated from a single CF. Both basket cells and stellate cells provide an inhibitory (GABAergic) entry to the PuC, with cells in the basket synapse to the initial segment of the PuC axon, and stellate cells to the dendrites [60, 61].

Presynaptic KARs participate in plasticity in the cerebellum where PF synapses onto PuCs mediate a form of LTD that is affected by the paired activation of CFs [62], **Table 1**; of these two types of fibers (PF and CF synapsing onto the same cells (PC), only PF have presynaptic KARs [62], similar to other brain regions as somatosensory and visual cortices in which fibers containing and noncontaining presynaptic ionotropic glutamate receptors synapse onto the same postsynaptic cell and induce LTD [63–69]. The exact role and action mechanism of KARs mediating LTD in the cerebellum are not well known yet and await further investigation.

The proper cerebellum development depends on a precise coordinated sequence of postnatal events, some of which are mediated by glutamate receptors. For example, NMDA receptors have been implicated in the migration of granular cells [70] and in the synaptic pruning of climbing fibers [71]. Although it has recently been shown that KARs are involved in synaptic transmission, little is known about their role in development. However, the expression of kainate-type glutamate receptor subunits in immature granule cells of the outer germinal layer of the developing cerebellum suggests that KARs may also have a role in neuronal maturation. Throughout the maturation process of the cerebellum, the quantity, composition, and function of KARs vary. Initially, cerebellar granular cells have a minimal amount of AMPARs in the postnatal period compared to KARs, which are predominant in immature granule cells. Different studies have shown that KARs composed of subunits GluK1, GluK2, and GluK5 predominate, and over the period of development, an increase in the number of KARs is observed and once the adult stage is reached, the number of KARs containing GluK1 subunits suffers a reduction in their expression in the granular layer, while the GluK2 and GluK5 remain constant, in contrast to AMPARs that increase their number, constituting a very notable majority compared to KARs.

KARs' activation	High concentrations of kainate	Depression of glutamatergic synaptic transmission	Delaney and Jahr [86]
	Low concentrations of kainate	Facilitation of glutamatergic synaptic synaptic transmission	Falcón-Moya et al. [80]
	Ionic imbalance	Calcification	Korf and Postema [78]
	Increase in Ca^{2+}	Neurodegeneration	
	Nodular cerebellum lesion Putrescine increase Histological damage	Ataxia	Maiti et al. [72] de Vera et al. [73] Yamaguchi et al. [74] Andoh et al. [75]
Parallel fibers paired with postsynaptic depolarization	Presynaptic KARs' activation	Long-term depression	Crépel [62]
Increase of GluR6 and GluK2 receptors	Reduction of GABAergic activity	Schizophrenia	Harrison et al. [76] Bullock et al. [77]

Table 1.
KARs' actions in the cerebellum.

All of these findings suggest that KARs have an important role in the development process of the cerebellum. Some indications suggest that GluK1-containing KARs participate in cerebellar development in the beginning of the differentiation of granular cells.

Additionally, KARs have been involved in some brain alterations in the cerebellum and a direct relationship exists between KA injection and cerebellar ataxia. Thus, the cerebellum is an important target to study functions of KARs and its possible role causing ataxia [72–75]. Furthermore, in patients with schizophrenia, an increase in KARs containing GluR6 and K2 subunits is observed, which would mediate a reduction in GABAergic transmission [76, 77]. In neurodegeneration, KARs may have a role in calcification of the brain tissue as it has been found that local application of KA in some areas of the cerebellum produces changes in different ion levels, highly increasing Ca^{2+} levels for more than 8 weeks, which mediate calcification [78] (**Table 1**). KARs have been described as producing increases in intracellular calcium [79, 80] and seems to signal increasing intracellular calcium without putting the cell at risk due to excitotoxicity, due to its low conductance in contrast to AMPARs. Due to the lack of knowledge on the subject, further exploration is necessary to determine the KARs' role in cerebellum development and cerebellar alterations.

2.1 KARs modulating glutamate release in the cerebellum: a biphasic effect

KARs are known to be expressed in the cerebellar cortex in the axons of cerebellar granule cells that form PF and make excitatory synapses with PuC [58]. Messenger RNA transcripts encoding for different KAR subunits and functional expression of KAR subtypes have been reported [81–84]. Biophysical studies with single-channel recording have shown GluK1 activity [85], suggesting these KARs are Ca^{2+} permeable. A biphasic action of KARs, activated by the agonist domoate, has been shown previously at PF-PuC synapse, with low agonist concentrations, facilitating synaptic transmission and higher concentrations depressing synaptic

transmission [86] in agreement with what has been found in the hippocampus [87–89], cortex [90], amygdala [91], and the thalamus [92]. EPSC trial-to-trial fluctuation analysis, failure rates, as well as paired-pulse ratios have shown that these facilitatory and depressive actions of KARs in the cerebellum are mediated by presynaptic KARs [80]. However, the precise mechanism of action by which KARs mediate potentiation (and depression) of synaptic transmission at PF-PuC synapses has remained elusive until very recently [80] (**Table 1**).

2.1.1 Action mechanism for KARs-mediated facilitation of glutamate release at cerebellar PF-PuC synapses

We have recently demonstrated that the effect of the KARs' activation in this synapse requires protein kinase A (PKA) activation, since the inhibition of this protein by cAMP-Rp suppresses the effect of KA in glutamate release [80], in agreement with previous studies in hippocampus and cortex [87–89]. This congruence between mechanisms at different synapses has also been seen through the inhibition of PKA using H-89, which eliminates KARs-mediated facilitation of glutamate release. Similarly, the direct activation of AC (adenylyl cyclase) using forskolin caused an elimination of facilitation when KARs were activated by KA (with NMDARs and AMPARs blocked). These data indicate that a signaling mediated by AC/cAMP/PKA supports the facilitation of the modulation of synaptic transmission/glutamate release in these cerebellar synapses (**Figures 1–3**).

As observed in other synapses, Ca^{2+} seems to play a fundamental role in facilitating glutamate release at PF-PuC synapses. By blocking calcium-permeable KARs by the selective inhibitor philanthotoxin, KAR-mediated synaptic facilitation of glutamate release was prevented, indicating that there is a strict requirement for external Ca^{2+} entry through KARs to support the facilitation effect observed on glutamate release, indicating that KARs mediating the facilitation of glutamate release are calcium permeable [80].

Additionally, as has been reported at hippocampal synapses, the depletion of intracellular Ca^{2+} stores by a treatment with thapsigargin (a noncompetitive calcium inhibitor of the sarcoplasmic reticulum ATPase) eliminates the facilitation of glutamate release mediated by KARs' activation. The same result was found when selectively inhibiting Ca^{2+}-induced calcium release by using ryanodine, indicating that the entry of Ca^{2+} via KARs induces a mobilization of Ca^{2+} from the intraterminal Ca^{2+} reserves to mediate the increase in glutamate release observed [80].

Furthermore, it has been observed that the facilitation of glutamate release mediated by the activation of KARs is sensitive to calmodulin inhibitors. Previous studies showed that the increase of cytosolic calcium levels activates Ca^{2+} dependent on AC present in the terminals of parallel fibers. Through treatment with the calmodulin inhibitors, W-7 and calmidazolium, it has been recently shown [80] that the inhibition of calcium-calmodulin function prevents KAR-mediated presynaptic facilitation of glutamate release in cerebellar slices, supporting the hypothesis that after KAR activation and cytosolic elevation of Ca^{2+}, a calmodulin-dependent calcium coupling activates AC, which subsequently activates the AC/cAMP/PKA pathway, thus promoting synaptic facilitation through an increase in neurotransmitter release at PF-PuC synapses [80].

2.1.2 Action mechanism for KARs-mediated depression of glutamate release at cerebellar PF-PuC synapses

Recently, in the same study discussed in the previous section [80], a transient synaptic depression of glutamate release with high concentrations of KA (3 μM)

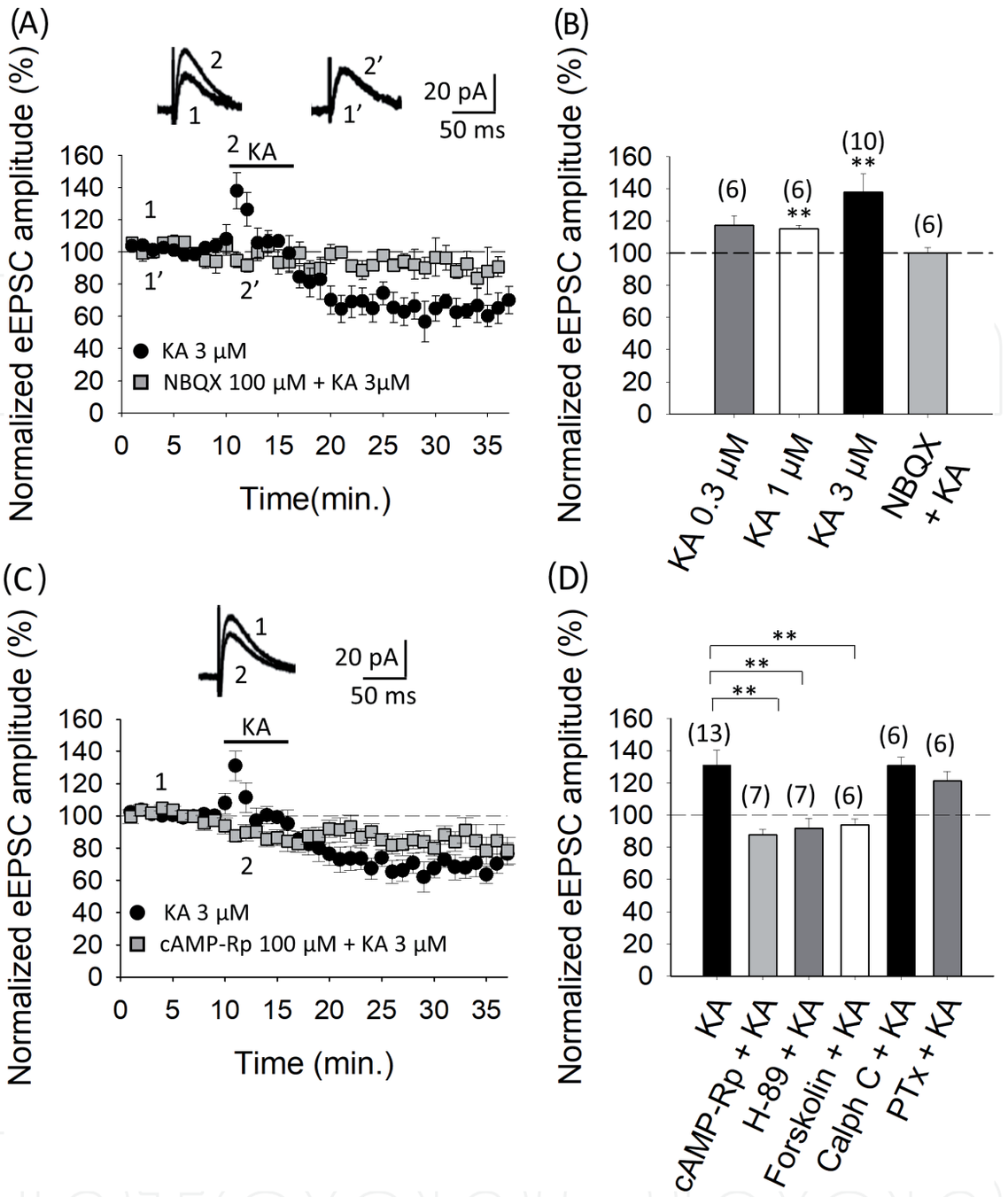

Figure 1.
KAR-mediated facilitation of glutamate release involving activation of adenylyl cyclase (AC) and downstream protein kinase A (PKA) at PF-PuC synapses of the cerebellum. (A) Time course of KA (3 µM) effect on eEPSCs amplitude in the absence (circles) and presence of NBQX (squares). Insets show traces before and after 4 min of KA perfusion in the absence (1, 2) and in the presence of 10 µM NBQX (1', 2'). (B) Quantification of modulation observed in (A) and dose-response curve. (C) Time course of the effect of KA on eEPSC amplitude in cAMP-Rp-treated slices. (D) Inhibition of PKA by cAMP-Rp (100 µM) or H-89 (2 µM), and activation of AC by forskolin (30 µM) prevented the facilitatory action of KA. Inhibition of PKC with calphostin C (1 µM) has no effect on the KA enhancement of the eEPSC amplitude. The facilitatory effect of KA is not affected in slices treated with pertussis toxin. Modified from [64].

was observed as reported for other different brain areas including thalamus, cortex, hippocampus, and amygdala [89–92]. This depression of glutamate release was prevented in the presence of cAMP-RP (which inhibits the activation of PKA), but was not affected by any other experimental modification discussed above with respect to the facilitation of glutamate release. This fact may indicate that the synaptic depression is probably related to an AC/cAMP/PKA signaling pathway (as for facilitation of glutamate release), but without the coupling of Ca^{2+} to the AC. Therefore,

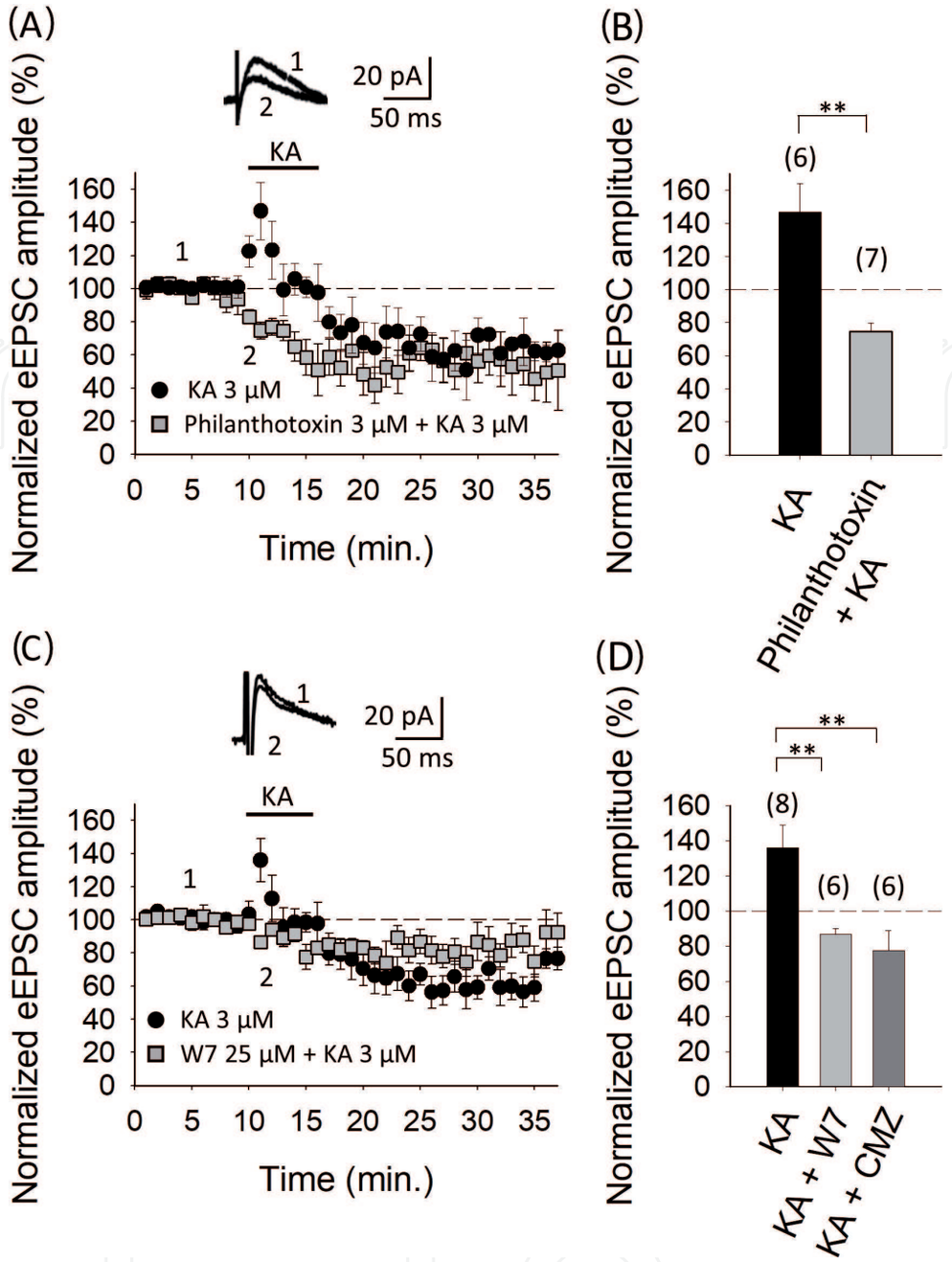

Figure 2.
Facilitation of glutamate release mediated by KAR activation requires an increase of Ca^{2+} in the cytosol and Ca^{2+} calmodulin at cerebellar PF-PuC synapses. (A) Time course of KA (3 µM) effect on eEPSCs amplitude in control condition (circles) and in slices treated with philanthotoxin (squares). (B) Quantification of modulation observed in (A). (C) Time course of KA (3 µM) effect on eEPSCs amplitude in control condition (circles) and in the slices treated with 25 µM W-7 (squares). (D) Quantification of modulation observed in (A) and in the presence of 1 µM CMZ. Modified from [64].

KA receptors have alternative mechanisms for facilitating and depressing glutamate release at PF-Pu synapses (**Figures 1–3**). In previous studies, investigating mossy fiber-CA3 hippocampal synapses [88, 89, 93, 94], as well as the amygdala [37] and cortex [36], a similar mechanism has been observed additionally involving the activation of a G-protein for the depressive effect that may well be also the case for these cerebellar synapses.

Although the presynaptic function of KARs facilitating glutamate release implies an increase in AC/cAMP/PKA signaling induced by the calcium calmodulin complex, KARs appear to be negatively associated with this pathway to carry out synaptic transmission of depression. Previous studies at hippocampal MF-CA3

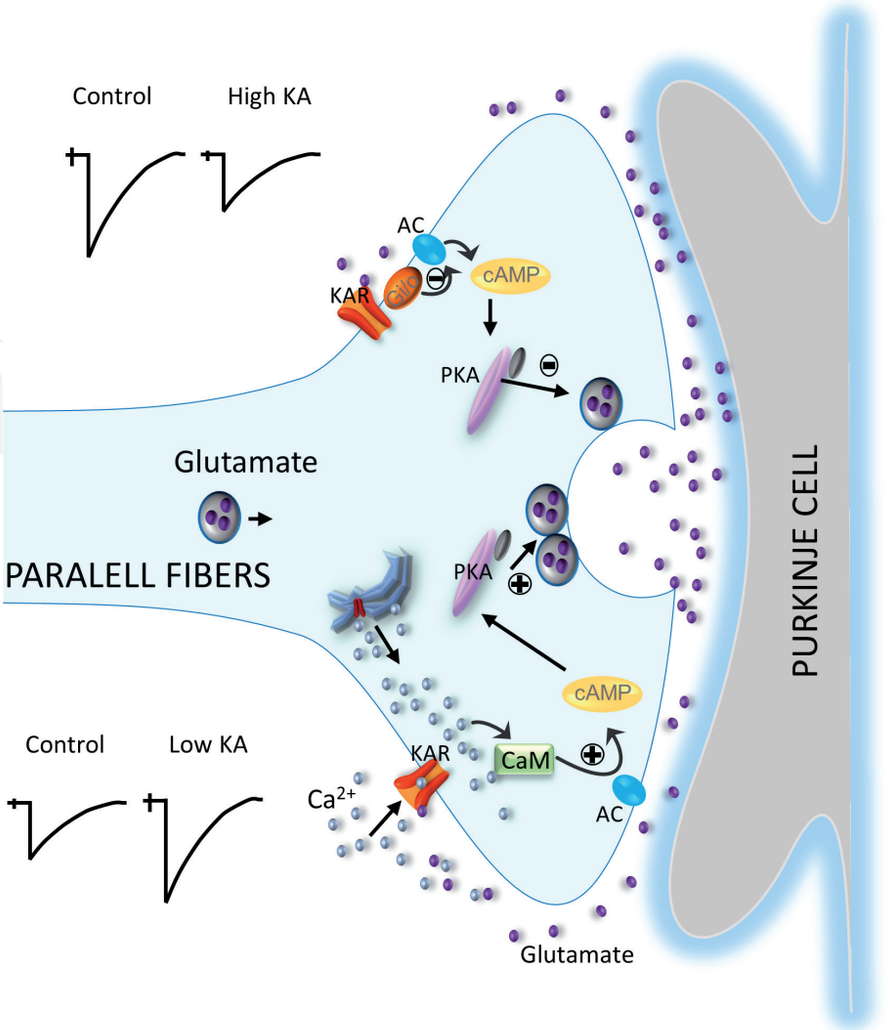

Figure 3.
KAR-mediated modulation of glutamate release in the cerebellum. Actions of KARs depressing or facilitating glutamate release at the PF-PuC synapse. KAR activation by high concentrations of KA (>3 μM) depresses glutamate release at PF-PuC synapses, an effect that involves $G_{i/o}$ protein and the adenylate cyclase/cAMP/protein kinase A (AC/cAMP/PKA) pathway. KAR activation by low concentrations of kainate (<0.3 μM) only facilitates glutamate release following activation of a Ca^{2+}-calmodulin/AC/cAMP/PKA pathway.

synapses and thalamocortical synapses, as well as at PF-PuC synapses, have reported that the depression of glutamate release mediated by presynaptic KARs occurs through a negative coupling to the AC/cAMP/PKA pathway, being actually evoked by the action of a PTx-sensitive protein G [80, 88, 92]. Despite the hypotheses discussed above, it is also possible that these observed mechanisms reflect the presence of two different types of KARs, a clear objective being to clarify this hypothesis in future studies.

3. Conclusions

Regarding the role and mechanisms of KARs in the modulation of glutamate release in the cerebellum, new and recent data indicate that the KARs effecting facilitation of glutamate release and synaptic transmission show a mandatory dependence on adenylyl cyclase (AC) and cAMP-mediated protein kinase A (PKA) activity. Furthermore, the KAR-mediated facilitation of transmission is contingent on both external Ca^{2+} permeation into the cytosol through KAR and repletion of

intracellular Ca^{2+} stores. Finally, a major sensitivity of facilitation to calmodulin inhibition suggests that KARs are coupled through a Ca^{2+}-calmodulin/AC/cAMP/PKA pathway at PF-PuC synapses in the cerebellum. KARs seem to use the inhibition of the AC/cAMP/PKA pathway to mediate a depression of glutamate release at the same synapses, but the activation of the AC does not involve calcium calmodulin and seems to be directly activated by a PTX-sensitive G protein.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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