Kainate receptors in the CA2 region of the hippocampus

Yuniesky Andrade-Talavera, Antonio Rodríguez-Moreno

The hippocampus is involved in important brain functions such as learning, memory, navigation, fear processing, and social behavior (Dudek et al., 2016). The most prominent areas of the hippocampus are typically denoted as the dentate gyrus and the three areas of cornu ammonis (CA1, CA2, and CA3). Discovered by Lorente de Nó (1934), the CA2 region of the hippocampus is a relatively small area interposed between CA1 and CA3 that forms the input linking the entorhinal cortex to the output of CA1 (Chevalley and Siegelbaum, 2010). Although very little is known about the function of CA2 in detail (Hitti and Siegelbaum, 2014; Dudek et al., 2016), it is currently increasing interest in its physiology and cumulative evidence indicates that this hippocampal area may have important and unique properties as it participates in engagement, neurogenesis, and information processing (Hainmueller and Bartos, 2018; Pang et al., 2019; Middleton and Mchugh, 2020; Lehr et al., 2021). Recent discoveries have revealed that CA2 is involved in the formation of social and spatial/temporal memories (Hitti and Siegelbaum, 2014; Dudek et al., 2016). The CA2 region, therefore, the CA2 network seems to play a critical role in balancing levels of excitation and inhibition in the hippocampus (Barnett et al., 2018). Notably, importantly, excitation/inhibition imbalances have been implicated in the diverse brain and neurodevelopmental disorders.

The physiological presence of glutamate receptors of the kainate type (kainate receptors, KARs) in the CA2 region of the hippocampus has long been demonstratet (Falcón-Moya et al., 2021). In the hippocampus, as in other brain regions, KARs are located postsynaptically participating in synaptic (NMDA and mGluR) and presynaptically modulating neurotransmitter release at different synapses (Silha and Rodríguez-Moreno, 2013). Additionally, they participate in synaptic plasticity (Negrete-Díaz et al., 2007; Lyon et al., 2011) and their inadequate activation may produce brain alterations such as epilepsy (Falcón-Moya et al., 2018). KARs are involved in the control of GABA and glutamate neurotransmission underlying mechanisms at CA1 and CA3 (Rodríguez-Moreno and Silha, 2011, 2013; Negrete-Díaz et al., 2021). KARs can be used to modulate a depression of glutamate release at CA3 Schaffer collaterals (SC)-CA1 synapses and, for the moment, no mediated facilitation has been described at these synapses. At SC-CA2 terminals, KARs-mediated depression of glutamate release is accompanied by a decrease of intracellular Ca\(^{2+}\) levels indicating that these terminals express KARs that operate in a metabotropic mode of action. This operational mode provokes a reduction of voltage-gated Ca\(^{2+}\) channels (VGCC) activity, thereby inhibiting glutamate release. By contrast, at mossy-fibers (MF)-CA3 synapses they have a biphase mode of action regulating glutamate release, with low agonist concentrations facilitating synaptic transmission, and higher concentrations modulating a depression of synaptic transmission (Rodríguez-Moreno and Silha, 2013). Presynaptic KARs-mediated facilitation of glutamate release at MF-CA3 synapses involves a cytosolic Ca\(^{2+}\) increase through Ca\(^{2+}\)-permeable KARs that downstream triggers Ca\(^{2+}\)-induced Ca\(^{2+}\)-release from internal stores. The mechanisms involved in this facilitation include both mGluR-dependent and mGluR-independent pathways involving cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) cascade. The inhibitory action of PKA on SC-CA2 synapses has been described (Hitti and Siegelbaum, 2014; Hitti et al., 2010). This mechanism, however, is not specific to the CA2 region of the hippocampus. Moreover, G\(_{i}\) proteins have been previously involved in KARs signaling since the discovery of its role in KAR-mediated modulation of GABA release in the hippocampus (Negrete-Díaz et al., 2018). Notably, a role of G-protein in KARs-mediated modulation of glutamate release has also been described in the hippocampus at SC-CA3 synapses. KARs are normally quite reduced in magnitude. This is quite different from those in CA1 and CA3. The reasons for this are not yet clear but may be related to molecular or genetic differences as they exhibit distinctive gene expression patterns. Additionally, and interestingly, synapses onto CA2 neurons do not enter into the cytoplasm from the extracellular side nor calcium from internal stores to mediate their function modulating glutamate release. To what extent this is due to or is a consequence of CA2 neurons is still open to debate and controversy, for instance, at SC-CA2 and MF-CA3 synapses. To examine the requirement of Ca\(^{2+}\) in KARs-mediated depression of glutamate release, the authors investigated the effects of nifedipine, which selectively blocks L-type VGCCs, and ryanodine that prevents Ca\(^{2+}\)-induced Ca\(^{2+}\) release from thapsigargin in these cells. These experimental approaches failed to prevent KARs-mediated decrease of glutamate release at SC-CA2 synapses. This contrast with L-type VGCCs and Ca\(^{2+}\) mobilization from internal stores have no role in the synaptic depression observed at SC-CA2 synapses following KAR activation (Figure 1).
CA2 neurons are more resistant to injury than CA3 and CA1 neurons that are quite sensitive and vulnerable to seizures, traumas, and ischemic insults. Epilepsy normally produces loss of pyramidal neurons, but CA2 cells are resistant with less cell loss observed after epilepsy. The presence of KARs at SC-CA2 synapses highlights the need to further research dissecting the putative role of the described KAR in the CA2 region mediating a decrease in glutamate release after exposure of increasing glutamate concentrations and their role promoting neuronal network stability as opposed to the known involvement of KARs in epilepsy (Falcón-Moya et al., 2018).

In conclusion, KARs are functionally present at SC-CA2 excitatory synapses and the presynaptic activation of KARs by KA at these synapses produces a depression of synaptic transmission and a decrease in the amount of glutamate released. Mechanistically, KAR-mediated presynaptic depression involves the activation of a G-protein that would signal the activation of AC to reduce CaMP levels to mediate a decrease in glutamate release and, therefore, in synaptic transmission at the SC-CA2 PC synapses of the hippocampus. Whether KARs present in the CA2 region of the hippocampus have a role in social behavior or spatial or temporal memories requires further experimentation, but modulating glutamate release, KARs may directly control or affect excitation/inhibition ratio that may be involved in different functions including the proper network performance and their behavioral outcomes.

Future directions: The determination of the presence of functional KAR in the CA2 region of the hippocampus advances our understanding of the widespread presence of KARs in pivotal brain structures, subregions, and synapses. Although this study by Falcón-Moya et al. (2021) brings a kind of starting cornerstone in the field of KAR functions in this overlooked but relevant hippocampal region, it reveals that much research is needed in this field to provide answers to remaining questions such as 1) Do KARs have a role in plasticity in the CA2 region of the hippocampus? 2) Are gial cells in the CA2 region involved in the resistance to damage of this region and, should it be the case, are KARs involved? 3) Do KARs play a role in CA2 during development? In addition, in future studies, a possible facilitation of glutamate release and the mechanism involved should be investigated in this synapse to determine whether the aforementioned bimodal regulation of neurotransmitter release by KARs is a general mechanism or not. Moreover, in adults, modulation involves PKA and the AC/CAMP/PKA pathway. The substrate for PKA-mediated phosphorylation that underpins the decrease in glutamate at this area remains to be determined.

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Yuniesky Andrade-Talaver, Antonio Rodríguez-Moreno
Laboratorio de Neurociencia Celulary Plasticidad, Departamento de Fisiología, Anatomía y Biología Celular, Universidad Pablo de Olavide, Sevilla, Spain
*Correspondence to: Antonio Rodríguez-Moreno, PhD, arodmoro@upo.es.
https://orcid.org/0000-0002-8078-6175 (Antonio Rodríguez-Moreno)

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