Kainate receptors in the developing neuronal networks

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\textbf{ABSTRACT}

Kainate receptors (KARs) are highly expressed in the immature brain and have unique developmentally regulated functions that may be important in linking neuronal activity to morphogenesis during activity-dependent fine-tuning of the synaptic connectivity. Altered expression of KARs in the developing neural network leads to changes in glutamatergic connectivity and network excitability, which may lead to long-lasting changes in behaviorally relevant circuitries in the brain. Here, we summarize the current knowledge on physiological and morphogenic functions described for different types of KARs at immature neural circuitries, focusing on their roles in modulating synaptic transmission and plasticity as well as circuit maturation in the rodent hippocampus and amygdala. Finally, we discuss the emerging evidence suggesting that malfunction of KARs in the immature brain may contribute to the pathophysiology underlying developmentally originating neurological disorders.

\section{Introduction}

The research conducted during the last few decades has revealed that the functions of kainate receptors (KARs) are in many respects unique within the family of ionotropic glutamate receptors (AMPA-, NMDA-and KA-receptors), which mediates fast excitatory neurotransmission in the brain. KARs mediate ionotropic postsynaptic responses only at certain synapses and instead have predominant functions in modulation of neurotransmitter release and neuronal excitability (reviewed by Lerma, 2003; Jane et al., 2004; Pinheiro and Mulle, 2006; Contractor et al., 2011; Lerma and Marques, 2013; Carta et al., 2014; Evans et al., 2019). KAR activation can lead to long-lasting changes in synaptic structure and function, and contribute to long-term potentiation (LTP) and long-term depression (LTD) in various areas of the brain (e.g. Bortolotto et al., 1999; Park et al., 2006; Shin et al., 2010; Clarke et al., 2014; Koga et al., 2015). Many of the modulatory actions of KARs are mediated via G-protein coupled mechanisms, which expands the signaling capacities of KARs beyond the fast ionotropic actions (reviewed by Valbuena and Lerma, 2016).

KARs are heavily expressed during the early postnatal life, during the time the synaptic circuitry is constructed and fine-tuned in an activity-dependent manner (Bahn et al., 1994; Ritter et al., 2002; Ryazantseva et al., 2020). Hence, it has been suggested that KARs regulate transmission and plasticity during period of activity-dependent circuit refinement and thereby influence development and maturation of the neuronal connections (reviewed by Hanse et al., 2009; Lauri and Taira, 2011; Lauri and Taira, 2012). Such functions for pre-and postsynaptic KARs have been described in several areas of the immature brain, including the barrel cortex (Kidder and Issak, 1999; Kidder et al., 2002; Bannister et al., 2005; Jouhanneau et al., 2011), the spinal cord (Lee et al., 2001; Stegenga and Kalb, 2001; Joseph et al., 2011), the superior colliculus (van Zundert et al., 2010), the hippocampus (Lauri et al., 2005, 2006, 2006; Maingret et al., 2005; Sallert et al., 2007; Caiati et al., 2010; Juuri et al., 2010; Segerstrale et al., 2012; Clarke et al., 2014) and the amygdala (Ryazantseva et al., 2020). Interestingly, in all these brain areas, KARs have developmentally restricted functions that are tightly associated with a transient stage of synapse maturation. These mechanisms are thought to facilitate activity-dependent fine-tuning of the circuitry either indirectly, via regulating excitation-inhibition balance and NMDA-receptor activation at the immature networks, or by directly mediating plasticity related signals at the level of individual synapses (Hanse et al., 2009; Lauri and Taira, 2011, 2012). Additional evidence from various cultured preparations implies that KAR signaling may...
2. Expression pattern of KARs in the developing brain

KARs are composed of five subunits, designated GluK1 – 5 (Grik1-5), that can be grouped into low-affinity (GluK1–3) and high-affinity (GluK4–5) subtypes. The subunits co-assemble in diverse combinations to form functional tetrameric receptors with distinct pharmacological and biophysical properties (reviewed by Perrais et al., 2006; Jane et al., 2009). Additional variation is created by alternative splicing of the subunits GluK1-3 and RNA editing of the subunits GluK1 and GluK2 (reviewed by Huettner, 2003; Pinheiro and Mulle, 2006; Evans et al., 2019), as well as interaction with the auxiliary subunits, neuropilin and tolloid-like 1 (NETO1) and NETO2 (Copits and Swanson, 2012).

Expression pattern of various KAR subunits in the brain has been mainly studied at the mRNA level, because antibodies able to reliably detect KAR subunits in the native tissue are scarce. KAR subunit mRNA expression can be detected in the rodent brain during embryonic development and most subunits show a peak in their expression during late embryonic or early postnatal period, co-inciding with the period of intense synaptogenesis (Bahn et al., 1994; Lilliu et al., 2002; Ritter et al., 2002; Ryazantseva et al., 2020). In the adult stage, subunits GluK2 and GluK5 are abundantly expressed in various areas of the brain, while the subunits GluK1, GluK3 and GluK4 are restricted to certain cell types and/or developmental stages (Wisden and Seeburg, 1993; Bahn et al., 1994; reviewed by Huettner, 2003; Hadzik et al., 2017). RNA sequencing data from adult cortical neurons supports that excitatory neurons strongly express KAR subunits GluK2,3 and 5 while subunits GluK1,2,3 and 5 are expressed in various different types GABAergic interneurons, apparently in an unspecific manner (Cauli et al., 2000; Fuzik et al., 2016; Huntley et al., 2020). GluK4 expression is very low in the adult neocortex and mainly restricted to the hippocampus (Kask et al., 2000; Arora et al., 2018).

The developmental expression pattern of KARs is best characterized in the hippocampus, where mRNA encoding for all subunits GluK1-5 can be detected at glutamatergic principal neurons during early postnatal development (Wisden and Seeburg, 1993; Bahn et al., 1994; Ritter et al., 2002, Fig. 1). Towards adult stage, expression of GluK3 is strongly downregulated and restricted to dentate gyrus, GluK4 becomes mainly confined to principal neurons in area CA3 and GluK1 to GABAergic interneurons (Bahn et al., 1994; Ritter et al., 2002; Kask et al., 2000; Vesikansa et al., 2012, Fig. 1). In the adult, GluK1, GluK2 and GluK5 mRNAs have been detected in somatostatin (SOM)-, cholecystokinin (CCK)/cannabinoid receptor 1 (CB1)-, and parvalbumin(PV)-expressing subsets of GABAergic interneurons (Wyeth et al., 2017). Thus, subunits GluK2/5 are strongly expressed in both glutamatergic and GABAergic neurons throughout development, while GluK3 and GluK4 shift from broad to localized expression pattern in parallel with maturation of the circuitry. GluK1 mRNA, on the other hand, is detected both in principal neurons and in GABAergic interneurons in the hippocampus during the first week of life, while in the adults, its expression is predominant in GABAergic interneurons (Vesikansa et al., 2012). This shift in expression pattern can be attributed to developmental loss in expression of GluK1c splice variant, which is preferentially detected in pyramidal neurons in the neonatal hippocampus (Vesikansa et al., 2012).

The extent of GluK1 and GluK2 RNA editing changes during the late embryonic and early postnatal stages (Paschen et al., 1997; Bernard et al., 1999). Q/R editing converts glutamine to arginine in the channel pore and results in reduced Ca2+ permeability of the receptors. At embryonic stages and at the time of birth, most of the GluK1/2 subunits are unedited and thus calcium permeable; but the proportion of edited subunit rapidly increases, reaching the adult levels during the first postnatal week. In the adult rat brain, the GluK2 subunit is about 90% edited and the GluK1 subunit is 40–60% edited (Paschen et al., 1997; Bernard et al., 1999).

### Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| ACC          | anterior cingulate cortex |
| AMPA         | α-Amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid |
| BD           | bipolar disorder |
| BDNF         | brain derived neurotrophic factor |
| BLA          | basolateral amygdala |
| CB1          | cannabinoid receptor 1 |
| CCK          | cholecystokinin |
| CeA          | central amygdala |
| EPSC         | excitatory postsynaptic current |
| GABA         | gamma-aminobutyric acid |
| IPSC         | inhibitory postsynaptic current |
| KAR          | kainate receptor |
| LA           | lateral amygdala |
| LTD          | long-term depression |
| LTP          | long-term potentiation |
| MDD          | major depressive disorder |
| NETO         | neuropilin and tolloid-like protein |
| NMDA         | N-methyl-D-aspartate |
| P            | postnatal day |
| PKC          | protein kinase C |
| PV           | parvalbumin |
| SOM          | somatostatin |
| SUMO         | small ubiquitin-like modifier |
| TrkB         | tropomyosin receptor kinase B |
Different types of KARs are targeted to specific subcellular compartments depending on a variety of cellular signals, creating a complex pattern of KARs that may be dynamically regulated in response to neuronal activity and during development (Jaskolski et al., 2005; Pinheiro and Mulle, 2006; Pahl et al., 2014; Evans et al., 2019). The exact subunit composition of pre- and postsynaptically located KARs varies between brain regions but also between different types of synapses within a local microcircuit (reviewed by Lerma, 2003; Pinheiro and Mulle, 2006; Carta et al., 2014). Data from knockout mouse models as well as biochemical, histological and pharmacological studies indicate that in the adult, postsynaptic KARs at CA3 glutamatergic neurons comprise subunits GluK2 and GluK4/5 (Carta et al., 2014; Straub et al., 2016), GluK2/5 in the cerebellum (Yan et al., 2013), GluK1/3/5 in the retina (Lindström et al., 2014), while GluK1 and GluK2 contribute to postsynaptic KAR mediated currents in the amygdala, anterior cingulate cortex (ACC), insular cortex, perirhinal cortex, spinal cord and in hippocampal GABAergic interneurons (Mulle et al., 2000; Kerchner et al., 2002; Cho et al., 2003, 2011; Wu et al., 2005; Koga et al., 2012). Presynaptically, all the subunits GluK1-5 have been implicated in regulation of neurotransmitter release, depending on the synapse type. For example, regulation of glutamate release in the hippocampal mossy fibre synapses depends on subunits GluK1-2/3 (Lauri et al., 2001; Pinheiro et al., 2007), while presynaptic KARs at immature CA3-CA1 synapses are composed of GluK1 as a heteromeric combination with the high affinity subunits GluK4/5 (Visikansa et al., 2012). GluK1 subunit containing KARs also regulate GABA release in a variety of interneuron subtypes both during development and in the adults (e.g. Clarke et al., 1997; Maingret et al., 2005; Daw et al., 2010; Lourenco et al., 2010). Thus, individual subunits lack functional specification, but may operate in pre- and/or postsynaptic sites, most likely depending on the selection of available interacting proteins within the cell (reviewed by Jaskolski et al., 2005; Pinheiro and Mulle, 2006).

3. Physiological functions of KARs in the immature circuitry

Most of our existing knowledge on the physiological functions of KARs originates from experiments in acute slice preparations from the brain of juvenile or adult rodents. The use of KAR-selective pharmacological tools as well as genetically modified mouse models has revealed that KARs can modulate synaptic transmission via pre- and postsynaptic mechanisms, depending on synapse type. Postsynaptic KAR responses (KAR EPSCs) are present only in a subset of synapses in the adult brain and they typically display slow kinetics, well suited for integration of synaptic responses (e.g. Vignes and Collingridge, 1997; Castillo et al., 1997; Frerking and Ohlinger-Frerking, 2002; Pinheiro et al., 2013). Presynaptic KARs on the other hand, are widely distributed in the brain and act both as autoreceptors and heteroreceptors, to bidirectionally regulate neurotransmitter release at glutamatergic and GABAergic synapses (Pinheiro and Mulle, 2008; Lerma and Margues, 2013; Sihra and Rodrigues-Moreno, 2013). Apart from its synaptic functions, KAR activation may profoundly influence neuronal excitability directly, via depolarization of the membrane potential or indirectly, via regulation of potassium channels mediating afterhyperpolarizing currents (Melyan et al., 2002; Segerstrale et al., 2010).

Some of the functions characterized for KARs in the adult brain operate similarly in the immature circuitry. For example, pharmacological activation of KARs results in robust increase in GABAergic activity in the neonatal, juvenile and adult hippocampus, due to ionotropic excitation of interneurons (Cossart et al., 1998; Frerking et al., 1998; Khalilov et al., 2002; Maingret et al., 2005; Lauri et al., 2005; Orav et al., 2006).
In addition, several developmentally restricted functions for KARs have been described and these typically coincide with the time of developmental reorganization and fine-tuning of the connectivity (e.g. Kidd and Isaac, 1999; Lauri et al., 2005, 2006; Sallert et al., 2007; VanZundert et al., 2010; Caiati et al., 2010; Ryazantseva et al., 2020).

3.1. Postsynaptic KARs at immature synapses

The contribution of KAR EPSCs to transmission during synapse maturation has been studied in detail in the hippocampal mossy fibre synapses (Marchal and Mulle, 2004; Lanore et al., 2012), in the barrel cortex (Kidd and Isaac, 1999; Bannister et al., 2005) as well as in the superior colliculus (VanZundert et al., 2010). At the mossy fibre synapses, KAR EPSCs are detected from postnatal day (P)6 onwards, emerging at the time when synaptic AMPAR mediated transmission is strengthened and starts to display mature characteristics, such as frequency facilitation (Marchal and Mulle, 2004; Lanore et al., 2012). In contrast, at thalamocortical synapses in the layer IV of the barrel cortex, KAR EPSCs are observed early in development, but transmission is converted from predominantly KAR-mediated to AMPAR-mediated during the critical period (around P7-8) (Kidd and Isaac, 1999). Detailed quantal analysis of the mechanisms involved indicated that this developmental switch is attributable to a reduction in the number of kainate synapses and a reciprocal increase in the number of AMPA synapses (Bannister et al., 2005). Whether similar switch from KAR-to AMPA containing synapses occurs in other cortical regions where KAR contribute to synaptic transmission (e.g. Cho et al., 2003; Wu et al., 2005; West et al., 2007; Koga et al., 2012) is not known.

Transient postsynaptic KAR involvement in neural development has also been observed in superficial visual layers of the rodent superior colliculus (SC), where KARs contribute to transmission at the time of eye opening, when the synaptic circuitry is rapidly modelled in an activity dependent manner (VanZundert et al., 2010). Here, KAR EPSCs emerge after addition of AMPAR to synapses. During the time synaptic KAR currents are observed (3-7 days after eye opening), the overall AMPA mediated transmission does not significantly change, but there is an increase in GABAergic transmission, reflecting ongoing maturation of the circuitry.

Although the sequential order of addition of different receptor types (i.e. KAR vs AMPA receptors) to the synapse seems to be divergent, the developmental presence of KARs seems correlate with the time of activity-dependent circuit refinement. It has been proposed that at immature stage, when AMPA currents are labile, postsynaptic KARs provide the necessary depolarization required for NMDA receptor activation (VanZundert et al., 2010; Kidd and Isaac, 1999) and thereby facilitate synaptic plasticity underlying activity-dependent fine-tuning of the connectivity. Alternatively, for example in the spinal cord (e.g. Lee et al., 2001), KARs themselves are calcium permeable during early development, and might thus initiate calcium-dependent signaling cascades driving maturation of the connectivity (Fig. 2A and B).

KAR EPSCs are also observed in hippocampal GABAergic interneurons (Cossart et al., 1998; Frerking et al., 1998) and detected already during the first postnatal week (Orav et al., 2019). While the relative contribution of AMPA and KARs to transmission during development has not been analyzed, there is evidence suggesting that KARs and AMPARs are located at distinct synapse populations in interneurons (Wondolowski et al., 2009) and further, that the KAR-only synapses depend on NETO1 expression (Orav et al., 2019). Lack of synaptic KAR signaling in NETO1 deficient CA3 interneurons had no apparent consequences on postnatal development of AMPAR-NMDAR-mediated synaptic transmission (Orav et al., 2019). This suggests that KAR-synapses at GABAergic interneurons are not developmental precursors of AMPA-containing synapses and rather represent a distinct population of synapses with predominant functions at the adult stage (Huxter et al., 2007; Clarke et al., 2012).

3.2. Presynaptic KARs at immature synapses

Similar to postsynaptic KARs, the contribution of presynaptic KARs to transmission is developmentally regulated. Thus, presynaptic KARs are tonically active and continuously modulate transmitter release at immature synapses during the neonatal period, but not in the juvenile/adult stage (Lauri et al., 2005; Caiati et al., 2010; Ryazantseva et al., 2020). Endogenous tonic activity of presynaptic KARs has been characterized in various synapses in the hippocampus (Lauri et al., 2005, 2006, 2006; Caiati et al., 2010) and more recently, in the amygdala (Ryazantseva et al., 2020) at the stage when the nascent synaptic contacts become functional. The prominent endogenous activation of
presynaptic KARs is a distinctive feature of the developing circuitry, typically observed during the first postnatal week in rodents and downregulated in parallel with maturation of the circuitry (Sallert et al., 2009; Ryazantseva et al., 2020).

The tonic activity of KARs (t-KAR) either inhibit or facilitate glutamate release depending on the synapse type. In a subset of immature CA3-CA1 synapses, presynaptic KARs are activated by ambient glutamate to maintain low probability of glutamate release. This allows substantial frequency-dependent facilitation of synaptic transmission in response to high-frequency activity (Lauri et al., 2006). Similar mechanism operates in basolateral amygdala (BLA), where t-KARs inhibit release in a developmentally restricted manner at glutamatergic inputs to principal neurons (Ryazantseva et al., 2020). Facilitation of glutamate release by endogenously active KARs has been described in GABAergic neurons both in the CA3 area of the hippocampus (Lauri et al., 2005) and in the central amygdala (CeA) (Ryazantseva et al., 2020) during early postnatal development (Fig. 2C and D).2

The first studies describing the t-KAR dependent regulation of glutamate release in the neonatal hippocampus found no evidence for heterosynaptic regulation of GABAergic transmission by endogenously active KARs (Lauri et al., 2005; Maingret et al., 2005). However, later on it was demonstrated that endogenous activation of presynaptic KARs reduces GABA release from immature mossy fiber terminals in the neonatal hippocampus (Caïati et al., 2010). Given the diversity of GABAergic interneurons, it is possible that the putative cell-type specific effects of t-KAR on GABA release are not observed when recording the bulk of spontaneous GABAergic currents (sIPSCs) from target neurons. Indeed, paired recordings have shown that presynaptic KARs regulating GABA release can be activated by synonymically released glutamate (Jiang et al., 2001; Lourenço et al., 2010) and further, that high-affinity presynaptic KARs might tonically inhibit GABA release from CCK/CB1 interneurons in the juvenile hippocampus (Wyeth et al., 2017). Rodent CCK/CB1 interneurons differentiate early in development and display adult-like physiological properties at the time of birth (Calvignoni et al., 2017), suggesting that t-KAR dependent regulation of GABA release might be operational already in the neonatal circuitry. However, confirmation of the developmental profile of the cell-type specific functions of KARs in GABAergic neurons awaits further studies.

3.2.1. Mechanisms underlying tonic presynaptic KAR activity and its regulation

The t-KAR mediated inhibition of glutamate release at immature synapses depends on activation of a G-protein mediated cascade that targets potential regulators of neurotransmitter release (Lauri et al., 2006; Sallert et al., 2007), while both ionotropic and G-protein coupled signaling has been implicated in facilitation of glutamate release (Lauri et al., 2005; Ryazantseva et al., 2020). Ionotropic facilitatory actions of presynaptic KARs have been attributed to modulation of action-potential evoked presynaptic Ca\(^{2+}\) transients, involving activation of calcium permeable KARs and/or KAR coupled release of calcium from intracellular stores (Kamiya et al., 2002; Lauri et al., 2003; Scott et al., 2008). The G-protein coupled actions of KARs on transmitter release are less well understood and may involve various developmentally regulated mechanisms, including PKC dependent regulation of presynaptic voltage–gated Ca\(^{2+}\) channels (Rozas et al., 2003; Sallert et al., 2007; reviewed by Lauri and Taira, 2012; Negrete-Díaz et al., 2018).

The subunit composition of KARs responsible for t-KAR activity is best characterized in the area CA1 of the hippocampus. Pharmacological evidence indicates that presynaptic t-KARs at CA3-CA1 synapses contain the GluK1 subunit (Lauri et al., 2005; Clarke et al., 2014). Moreover, these receptors are activated by relatively low agonist concentrations (Lauri et al., 2006), suggesting that the receptor tetramer also contains either or both of the high affinity subunits GluK4 and GluK5. In the hippocampus, pyramidal neurons express the GluK1c splice variant during early development, while GluK1b expression is restricted to interneurons (Vesikansa et al., 2012). Indeed, GluK1c expression pattern in the hippocampus corresponds well to pharmacological data on presynaptic t-KAR activity (Vesikansa et al., 2012). As axonal targeting of GluK1c depends on co-expression of GluK4 and NETO1 (Vesikansa et al., 2012; Orav et al., 2017), presynaptic t-KARs at CA3-CA1 are most likely composed of heteromeric GluK1c and GluK4 subunit containing receptors, interacting with the auxiliary subunit NETO1.

After the early postnatal period (>P10), presynaptic KARs are present at CA3-CA1 synapse, but these mature-type receptors are no longer tonically active (Clarke and Collingridge, 2002; Lauri et al., 2006). The developmental switch from immature t-KAR to mature-type KAR activity at CA3-CA1 synapses depends on BDNF/TrkB signaling (Sallert et al., 2009) and likely involves a change in their subunit composition (Vesikansa et al., 2012). The mature-type KARs are of lower affinity (Lauri et al., 2006) and thus less sensitive to ambient glutamate. In parallel, the levels of ambient glutamate decrease during circuit maturation, due to developmental increase in glial glutamate uptake mechanisms (e.g. Diamond, 2005; Hanson et al., 2019). At the CA3-CA1 synapses, the developmental mechanism for endogenous activation of KARs cannot be recapitulated simply by increasing the ambient glutamate concentration (Lauri et al., 2006). On the other hand, over-expression of GluK1c or GluK4 produces presynaptic t-KAR activity at a developmental stage when this activity is physiologically no longer observed (Vesikansa et al., 2012; Ryazantseva et al., 2020; Arora et al., 2018). Together, these data indicate that both a change in subunit composition and in ambient glutamate levels contribute to the developmental loss of t-KAR activity.

Intriguingly, in addition to the slow developmental downregulation, presynaptic KAR activity at immature CA3-CA1 glutamatergic synapses can be rapidly up- or down-regulated in response to different frequencies of neuronal activity (Lauri et al., 2006; Sallert et al., 2009; Clarke et al., 2014, Fig. 3). Specifically, t-KAR activity is irreversibly downregulated in response to induction of long-term potentiation (LTP), in a manner that depends on activation of the TrkB-receptor of BDNF (Lauri et al., 2006; Sallert et al., 2009; Clarke et al., 2014). On the other hand, LTD induction at the immature synapses results in an increase in KAR function, which involves high-affinity receptors and requires activation of NMDA receptors, nitric oxide (NO) synthetase, and post-synaptic calcium signaling (Clarke et al., 2014). The LTD-associated increase in KAR activity is developmentally restricted to immature CA1 synapses and lost after LTD induction, suggesting that it reflects a developmental stage of presynaptic lability, analogous to that described for postsynaptic AMPA-receptors at immature synapses (Hanse et al., 2009).

The molecular mechanisms underlying the rapid activity-dependent changes in t-KAR activity remain elusive. KAR surface expression is dynamically regulated by intracellular signals, including PKC-dependent phosphorylation and SUMOylation, which may rapidly downregulate functional KARs by targeting them to endocytosis (Park et al., 2006; Selak et al., 2009; Chamberlain et al., 2012). On the other hand, subcellular targeting of KARs involves various intracellular and transmembrane interacting proteins (Pahl et al., 2014; Evans et al., 2019), and such interactions also anchor and stabilize the receptors to synaptic sites. Reduced interaction with anchoring proteins, for example as a result of covalent modification, may rapidly disperse receptors away from synaptic sites leading to loss of synaptic function (Carta et al., 2013; Polenghi et al., 2020). These mechanisms have been described presynaptically, in the context of activity-dependent downregulation of KAR EPSCs in the mature circuitry; whether similar mechanism regulate presynaptic t-KAR awaits further studies.

3.3. KARs regulating excitability of the immature neuronal networks

Somatodendritic KARs may regulate cellular excitability via two ways: direct ionotropic depolarization of the target neurons, and G-protein coupled regulation of potassium channels that mediate
afterhyperpolarizing potential (I_{AHP}) (Melyan et al., 2002; Segerstråle et al., 2010). The first mechanism operates in both principal neurons and interneurons in the immature hippocampal circuitry. Even very low concentrations of kainate (50 nM) dramatically increase spontaneous action potential firing of CA3 pyramidal neurons, via axonal depolarization promoting ectopic spike generation (Juuri et al., 2010). Likewise, KAR mediated ionotropic depolarization of interneurons efficiently recruits GABAergic drive in the immature hippocampal circuitry, which is observed as a robust increase in spontaneous IPSCs in the principal neurons in response to pharmacological activation of KARs (Lauri et al., 2005; Maingret et al., 2005; Orav et al., 2019). The physiological significance of these mechanisms is not precisely characterized; for example, whether somatodendritic KAR in interneurons and/or pyramidal cells are activated during intense network activity and contribute to cellular depolarization and synchronization of the in the immature circuitry remains an open question.

While the developmental emergence of the KAR dependent regulation I_{AHP} in principal neurons is not known, a similar mechanism has been characterized in immature CA3 interneurons. In these cells, endogenously activated GluK1 subunit containing KARs tonically inhibit medium-duration afterhyperpolarization (mAHp) in a G-protein dependent manner, permitting a high interneuronal firing rate (Segerstråle et al., 2010). This mechanism is age dependent and disappears by the end of the second postnatal week, in parallel with maturation of the circuitry.

Thus, endogenous activation of KARs modulates the balance between excitatory and inhibitory transmission in the immature neural circuit via various mechanisms, operating in distinct cell types and subcellular compartments (Lauri and Taira, 2011). In the neonatal hippocampus, presynaptic GluK1 subunit containing KARs tonically inhibit glutamate release onto CA3 and CA1 pyramidal cells and facilitate release onto GABAergic interneurons (Lauri et al., 2005, 2006). In addition, endogenous GluK1 KAR activity upregulates the firing frequency of CA3 interneurons by inhibiting mAHp (Segerstråle et al., 2010). These mechanisms act to restrict asynchronous glutamatergic activity and increase GABAergic activity in the immature network (Lauri et al., 2005; Segerstråle et al., 2010). At the same time, however, dynamic activation of a distinct population of high-affinity axonal KARs increase network excitability by facilitating ectopic spike generation in the area CA3 (Juuri et al., 2010). Finally, synchronous glutamate release during network burst may activate somatodendritic KARs at GABAergic interneurons, to upregulate GABAergic transmission via ionotropic depolarizing action (Lauri et al., 2005; Maingret et al., 2005; Orav et al., 2019). Together, these various actions of KARs maintain the excitability of the immature hippocampal network at a level that permits the typical intrinsic patterns of synchronous network activity in the immature circuit (Lauri et al., 2005; Juuri et al., 2010; Lauri and Taira, 2011; Orav et al., 2019).

While the availability of selective antagonists have allowed studies related to physiological roles of GluK1 subunit containing receptors, the contribution of other types of KARs to neonatal network activity as well as the cell type specific mechanisms involved are less well understood. Since immature networks efficiently compensate for any changes in excitability (e.g. Desai et al., 2002; Huupponen et al., 2007, 2012), data from knockout mouse models is difficult to interpret. Yet, the finding that GluK2 deficient adult mice are resistant to KA induced seizures (Mulle et al., 1998), strongly suggest a critical role for GluK2 in regulation of network excitability in the neonatal brain where these receptors are strongly expressed. Consistently, recent data using local manipulation of KAR expression together with multicell array recordings indicate robust effects of GluK2 overexpression on spontaneous calcium oscillations in visual cortex slice cultures (Jack et al., 2019). Similar approach has been used to study the role of GluK1 in the hippocampus, revealing critical role for GluK1/NETO1 in developmental synchronization of CA3 and CA1 circuit (Orav et al., 2017; Kaarela et al., 2019).

### 3.4. KARs and synaptic plasticity at immature circuits

The diverse modulatory effects on both glutamatergic and GABAergic neurons enable KARs to efficiently regulate excitability and synchronization at the level of neuronal networks (reviewed by Lauri and Taira, 2011). Synchronous network activity provides the temporal structure that allows precise co-incidence detection of pre- and postsynaptic activity required for Hebbian – plasticity, such as LTP and LTD. At immature synapses, similar mechanisms are thought to initiate a cascade of signaling events that lead to stabilization and strengthening of appropriate connections and elimination of the excess ones (Zhang and Poo, 2001; Hua and Smith, 2004; Molnar et al., 2020).

Individual synapses transmit the high-frequency bursts of activity differentially, depending on their dynamic properties. Tonic activity of presynaptic KARs at immature CA3-CA1 synapses inhibits glutamate release probability and enables frequency dependent facilitation of synaptic transmission (Lauri et al., 2006). Thus, by maintaining low...
probability of glutamate release, presynaptic KARs enable immature synapses selectively to respond to the physiological high-frequency activity patterns. On the other hand, KAR mediated tonic inhibition of glutamate release reduces asynchronous activity, which might protect the immature synapse from pruning and elimination that is initiated by an LTD like process in response to continuous asynchronous activation (Hanse et al., 2009). Therefore, the tonic KAR activity improves the prospects for activity-dependent stabilization and strengthening of the immature synapse within a network that displays the typical patterns of intrinsic synchronous network bursts.

In addition to modulating the plasticity-inducing activity patterns, KAR signaling directly contributes to induction of LTP in various areas of the brain (e.g. Bortolotto et al., 1999; Shin et al., 2010; Cho et al., 2011; Koga et al., 2015; Petrovic et al., 2017). Calcium influx through presynaptic KARs contributes to LTP induction in the hippocampal mossy fibre synapse (Bortolotto et al., 1999; Lauri et al., 2003; Pinheiro et al., 2007), in thalamic inputs to lateral amygdala (LA) (Shin et al., 2010) and in the layer II/II in anterior circulate cortex (ACC, Koga et al., 2015). In the ACC, the presynaptic Ca2+ influx via GluK1 subunit containing KARs is proposed to activate the adenylcycl cyclase-protein kinase A (PKA) pathway, which then results in modulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels resulting in a long-lasting increase in glutamate release (Koga et al., 2015). Postsynaptically, depolarization and calcium influx via GluK1 subunit containing KARs mediates induction of LTP in convergent inputs to lateral amygudala (Cho et al., 2011). Postsynaptic GluK2 subunit containing KARs, on the other hand, may induce synaptic potentiation via G-protein dependent enhancement in synaptic recycling of AMPA receptors, which leads to increase in their surface expression (Petrovic et al., 2017).

Moreover, plastic changes in the synaptic function of KARs may contribute to expression of LTD and LTP either pre- or postsynaptically (Lauri et al., 2001; Park et al., 2006; Selak et al., 2009; Chamberlain et al., 2012; Carta et al., 2013), and similar mechanisms have been described at immature synapses (Kidd and Isaac, 1999; Lauri et al., 2006; Clarke et al., 2014). For example, at immature CA3-CA1 synapses, LTD induction results in loss of tonic KAR mediated inhibition of release, which contributes presynaptically to LTP expression during early development (Lauri et al., 2006; Luchkina et al., 2012). Vice versa, upregulation of presynaptic inhibitory KAR activity contribute to expression of LTD in a developmentally restricted period of synapse maturation (Sallert et al., 2007; Clarke et al., 2014). Although plasticity of KARs is not necessary for changes in synaptic efficacy at immature synapses, it significantly contributes to maturation of the transmission properties by modulating short-term plasticity. Hence, the existing data is consistent with the scheme where KAR expression at the immature state promotes plasticity driven by the endogenous activity patterns of the developing networks. After the period of activity-dependent circuit refinement, functional KAR are downregulated and synaptic transmission and plasticity becomes more controlled, suitable for their functions within the mature network.

4. Morphogenic and synaptogenic functions of KARs in the immature circuitry

The functions of kainate receptors in the developing neural circuits are diverse and not restricted to fast synaptic signaling. KARs influence morphological maturation of neurons in vitro (Marques et al., 2013; Jack et al., 2019) and in vivo (Ryazantseva et al., 2020), regulate neurite outgrowth and mobility of the axonal filopodia (Ibarretxe et al., 2007; Joseph et al., 2011; Chang and De Camilli, 2001; Tashiro et al., 2003), and mobilization of the synaptic vesicle in the growth cones (Gebrande et al., 2013). Moreover, evidence from in vitro studies suggests that both presynaptic and postsynaptic KARs also regulate synaptogenesis and synaptic maturation (Tashiro et al., 2003; Sakha et al., 2016; Petrovic et al., 2017).

4.1. KARs and maturation of neuronal morphology

The effects of KAR activation on morphological development of neurons has been mainly studied in vitro, using time lapse imaging and morphological analysis in cultured cortical, hippocampal and dorsal root ganglion (DRG) neurons (Chang and De Camilli, 2001; Tashiro et al., 2003; Monnerie and Le Roux, 2006; Ibarretxe et al., 2007; Joseph et al., 2011; Marques et al., 2013). In these models, pharmacological activation of kainate receptors regulates the motility of growth cones and axonal filopodia (Tashiro et al., 2003; Ibarretxe et al., 2007) as well as dendritic length (Monnerie and Le Roux, 2006; Joseph et al., 2011; Marques et al., 2013). The direction of the effect (i.e. stimulation or inhibition) depends on the developmental stage and on agonist concentration, likely reflecting activation of distinct receptor populations and downstream signaling mechanisms (Tashiro et al., 2003; Marques et al., 2013). For example, in DRG neurons, low concentrations of kainate enhance dendritic complexity and dendritic length (Monnerie and Le Roux, 2006; Marques et al., 2013) while high agonist concentrations result in growth arrest (Joseph et al., 2011; Marques et al., 2013). The growth inhibiting and growth promoting effect of KARs have been attributed to ionotropic and G-protein coupled signaling of KARs, respectively, that differentially regulate phosphorylation of the microtubule associated protein CRM2 (Marques et al., 2013). Based on these data, it has been suggested that in the early stages of circuit development, KAR activation increases neurite growth and the motility of filopodia, to facilitate dendritic growth and contact formation. When the contact is formed, the action of KARs switches from growth promoting to stabilizing, allowing maturation and differentiation of synaptic structures (Tashiro et al., 2003; Marques et al., 2013).

Few studies have described the effects of KARs on dendritic morphology in an intact tissue environment. In visual cortex organotypic culture, overexpression of GluK2 promoted growth and complexity of apical dendrites in layer II/II pyramidal cells and in interneurons, while NETO1 and GluK1 overexpression enhanced dendritic growth specifically in interneurons (Jack et al., 2019). GluK2 overexpression resulted in increased dendritic complexity also in neighboring wild-type neurons, suggesting that at least some of its effects were mediated indirectly, via enhanced network activity. Whether GluK1 directly regulates the dendritic maturation in interneurons remains an open question. Since presynaptic GluK1/NETO1 subunit containing KARs regulate glutamate release probability (Lauri et al., 2005, 2006, 2006; Orav et al., 2019; Ryazantseva et al., 2020), GluK1 overexpression in the principal neurons may enhance glutamatergic input to interneurons, which respond with dendritic growth. Such a mechanism has been recently shown in the postnatal amygdala, where developmental overexpression of GluK1 in the LA principal neurons, forming glutamatergic connections to CeA GABAergic neurons, leads to robust increase in their dendritic length and branching (Ryazantseva et al., 2020). Despite its pronounced effects on the efferent connectivity, GluK1 knockdown had no effect on dendritic morphology of the principal neurons (Ryazantseva et al., 2020). These studies imply that the roles of KARs in regulation of neuronal morphology are multifaceted, involving cell-type and subunit specific mechanisms that may act directly or indirectly, via changes in the circuit excitability.

4.2. KARs and maturation of glutamatergic synapses

Synapse development is characterized by a prolonged activity-dependent maturation phase that follows the initial contact formation. At glutamatergic synapses, maturation is triggered via an LTP – like mechanism that results in an increase in reliability and strength of transmission and involves changes in both presynaptic and postsynaptic properties (e.g. Isaac et al., 1995; Palmer et al., 2004; Luchkina et al., 2012). Involvement of KARs in formation, maturation and/or stabilization of excitatory synapses is supported by data from in vivo and in vitro models, showing that impaired KAR activity is associated with
delayed development of glutamatergic circuitry (Marchal and Mule, 2004; Vesikansa et al., 2007; Lanore et al., 2012; Sakha et al., 2016; Orav et al., 2017; Ryazantseva et al., 2020; Kesaf et al., 2020). While some of these effects may be mediated via KAR dependent changes in synchronous activity affecting plasticity induction, parallel evidence from dissociated cell cultures suggest that KAR signaling can directly influence synaptic differentiation and maturation both pre- and postsynaptically (Tashiro et al., 2003; Sakha et al., 2016; Petrovic et al., 2017).

4.2.1. Postsynaptic KARs

Several lines of evidence support that signaling via GluK2 subunit containing KARs promotes maturation of glutamatergic synapses and dendritic spines and that this mechanism is physiologically significant for appropriate development of synaptic connectivity in area CA3 (Marchal and Mule, 2004; Lanore et al., 2012; Kesaf et al., 2020). In GluK2 deficient mice, there is a marked delay in both functional and structural maturation of mossy fibre synapses (Marchal and Mule, 2004; Lanore et al., 2012), which is most clearly visible during the second postnatal week (P8–P14). On the other hand, local shRNA mediated knockdown of GluK2 results in changes in the morphology of dendritic spines in both primary hippocampal cultures in vitro and juvenile CA3 pyramidal neurons in vivo (Kesaf et al., 2020). Finally, application of KA, presumably activating GluK2 subunit containing KARs, increases the number of dendritic protrusions and maturity of spines in a calcium, G-protein and PKC dependent manner in primary hippocampal cultures (Petrovic et al., 2017). The same pharmacological treatment in area CA1 of the hippocampus induces synaptic potentiation that depends on metabotropic signaling via GluK2 subunit containing KARs (Petrovic et al., 2017).

GluK2 expression in spines is important for the proper dynamics of the actin cytoskeleton (Kesaf et al., 2020). Accordingly, GluK2 is reported to interact with several synaptic proteins involved in regulation of actin cytoskeleton, including β-catenin/N-cadherin complex, the cytoskeletal adapter 4.1N and profilin (reviewed by Lerma and Marques, 2013; Carta et al., 2014). Syntentin, a scaffolding protein interacting with GluK1b, GluK1c and GluK2a, is heavily expressed during the periods of synapse formation and stabilization and has been shown to regulate the number of dendritic protrusions, however, whether this requires a direct interaction with KARs remains unclear (Hirbec et al., 2005). GluK2 also binds to and regulates trafficking and surface expression of the KCl cotransporter KCC2 (Mahadevan et al., 2014; Pressey et al., 2017; Kesaf et al., 2020). KCC2 regulates morphology of dendritic spines and trafficking of AMPA receptors independent of its chloride transport function, through interactions with the actin cytoskeleton (Li et al., 2007; Gauvain et al., 2011). Interestingly, over-expression of KCC2 fully rescued the spine morphological changes following GluK2 knockdown (Kesaf et al., 2020), suggesting that KCC2 is one of the downstream effectors coupling KAR mediated glutamatergic signaling to changes spine morphology.

4.2.2. Presynaptic KARs

The roles of various KAR subunits in presynaptic development has been studied in detail using microfluidic culture system, where two neuronal populations are grown in isolation but connected by narrow tunnels allowing axon growth (Jokinen et al., 2013, Fig. 4A). Asymmetric genetic manipulation of KAR subunit expression in one of the chambers allows to study the specific roles axonal/presynaptic KARs in synaptic differentiation. Expression of the calcium permeable (Q) variants of low-affinity (GluK1–3) KAR subunits resulted in a large increase in density of synaptic vesicle clusters in isolated axons and was associated with robust increase in presynaptic efficacy, manifested as a high probability of glutamate release (Pr) and widening of the synaptic active zone (Sakha et al., 2016, Fig. 4). On the other hand, silencing expression of endogenous KARs (GluK2 and GluK5) caused a lower density of synaptophysin immunopositive puncta in microfluidically isolated axons. The effects of KARs on synaptophysin puncta were dependent on receptor activation, suggesting that KAR most likely acted by stabilizing immature sites that were already releasing glutamate. This is consistent with the idea that elevated signaling via calcium permeable KARs promotes presynaptic differentiation, possibly subsequent to motility inhibition (Tashiro et al., 2003; Ibarretxe et al., 2007; Joseph et al., 2011). GluK1 subunit containing presynaptic KARs are tonically activated at immature synapses (Lauri et al., 2006; Ryazantseva et al., 2020), and thus positioned to regulate synaptic maturation. Indeed, pharmacological and genetic evidence supports that presynaptic GluK1 KARs act as a physiological mechanism regulating formation of the glutamatergic circuitry both in the hippocampus and in the amygdala. The first findings supporting this idea were obtained using hippocampal cultured slices, where prolonged pharmacological blockade of endogenous GluK1 activity of resulted in a decrease in the number of functional glutamatergic synapses in area CA1, while a specific and enduring increase in

![Fig. 4. KARs regulate presynaptic differentiation and the strength of efferent connectivity. A. Schematic illustration of the microfluidic culture model. Hippocampal neurons are grown in two reservoirs that are connected by narrow microgrooves allowing axon growth. On one side, KAR expression is manipulated using lentiviral expression vectors. The side part of the tunnel contains isolated axons coming from both sides of the chamber. KAR expressing axons are identified with co-expression of GFP. On the uninfected side, manipulated axons crossing the tunnels make contact to wild-type dendrites. B. Visualization of the synaptic vesicle clusters at the isolated axons using synaptophysin (syn) staining indicates higher density of presynaptic puncta in axons expressing calcium permeable KAR subunits GluK1-3(Q) (K1–K3), while expression of GluK4 (K4), GluK5 (K5) or GluA2 (A2) had no effect. C. Co-Expression of ChR2 allows selective light-activation of the KAR expressing axons during patch–clamp recording of postsynaptic responses in the wild-type neurons. A significant increase in success rate of EPSCs indicates that axonal/presynaptic calcium permeable KARs enhance the strength of efferent connectivity (adapted from Sakha et al., 2016).]
A functional inputs was observed in response to treatment with GluK1 agonist ATPA (Vesikansa et al., 2007). Since GluK1 is sparsely expressed at the postsynaptic CA1 neurons, the effects were most likely due to altered activity of presynaptic KARs. More recently, it was shown that presynaptic targeting of GluK1 in hippocampal neurons depends on expression of the auxiliary subunit NETO1 (Orav et al., 2017). Consistent with a critical role of GluK1 in presynaptic differentiation, NETO1 deficient axons contained lower density synaptophysin puncta in comparison to controls, which was fully rescued by overexpression of GluK1 (Orav et al., 2017).

In the amygdala, t-KAR regulate transmission at glutamatergic projections from lateral (LA) to central amygdala (CeA) during the time the connectivity is rapidly forming (Ryazantseva et al., 2020). Local genetic inactivation of GluK1 in the LA during the developmental time of intense synaptogenesis impaired glutamatergic innervation and maturation of the target neurons in the CeA. Accordingly, GluK1 overexpression resulted in prolonged presynaptic GluK1 activity and strengthening of the LA-CeA glutamatergic connectivity. Interestingly, inactivation of GluK1 later on in development, when the receptors were no longer tonically active, had no effect on glutamatergic inputs to CeA (Ryazantseva et al., 2020, Fig. 5).

In summary, the existing literature supports that activity of different types of KARs can promote synaptic maturation, while their physiological impact on circuit development critically depends on the subcellular expression pattern as well as susceptibility for endogenous activation. Thus, genetic inactivation of GluK1 impairs maturation of glutamatergic connectivity during the time period these receptors are endogenously activated, but not later on in development (Ryazantseva et al., 2020). On the other hand, loss of endogenous GluK2 impairs synaptic maturation in the area CA3 of hippocampus (Marchal and Mulle, 2004; Lanore et al., 2012; Kesaf et al., 2020), where these receptors are strongly expressed and synaptically activated.

Expectedly, given the widespread expression of KAR subunits in the developing brain, the KAR dependent mechanisms regulating morphofunctional maturation of neurons are not restricted to the limbic circuits. Nevertheless, apart from the delay in development of the MF synapses in the GluK2 deficient mice (Lanore et al., 2012) and lower synapse density in striatum in GluK1-5 deficient mice (Xu et al., 2017), no major structural or morphological defects have been characterized in the constitutive knockout models of KAR. This suggests that KARs are not indispensable for morphological development of neurons, but their actions can be compensated for. Developing neural circuits are extremely plastic and can efficiently adapt to changes in excitability via various compensatory mechanisms; thus it is possible that such adaptive changes mask morphofunctional changes influencing network excitability in mice lacking KAR expression. Elucidation of the precise effects of KARs on neuronal development requires temporally controlled cell-type specific manipulations, for example via targeted genetic manipulation of individual subunits, which allows to dissect direct effects from the indirect consequences mediated by altered network activity.

Fig. 5. GluK1 KARs regulate glutamatergic innervation and maturation of central amygdala (CeA) neurons during the developmental period of intense synaptogenesis. A. Local inactivation of GluK1 expression in the basolateral amygdala (BLA) in Grik1 conditional knockout mouse using in vivo injection of GFP-CRE AAV virus at P2–P4. Ex vivo analysis of glutamatergic synaptic activity (mEPSC frequency) and dendritic morphology in central amygdala (CeA) neurons was performed at P21. GluK1 knockdown in the BLA resulted in significant loss of functional glutamatergic synapses in the CeA, observed as lower frequency of mEPSCs and lower density of dendritic spines. In addition, the number of dendritic intersections and the total dendritic length of CeA neurons were significantly lower in CRE injected mice as compared to controls. Scale bar, 50 μm. B. Similar data as in A, showing that local inactivation of GluK1 at a later developmental stage (P14 →) has no effect on synaptic density or dendritic morphology of CeA neurons. (Adapted from Ryazantseva et al. (2020); mouse images were adapted from SciDraw (https://scidraw.io/Galliano, Elisa (2020) https://doi.org/10.5281/zenodo.3926669; Kennedy, Ann (2020) https://doi.org/10.5281/zenodo.3925919).
5. Implications for developmentally originating neurological disorders

KARs have been linked to a number of neurodevelopmental disorders such as Down syndrome, major depressive disorder (MDD), bipolar disorder (BD), anxiety, schizophrenia, autism and obsessive compulsive disorder (Lerma and Marques, 2013). As for today, non-coding, intrinsic variants and de novo mutations located within KAR subunit genes have been associated with neurological diseases as well as with KAR genotype-dependent changes in cognition and response to antidepressant and antipsychotic treatments in humans. KAR genes, in particular Grik2, Grik3, Grik5 and Netro1, are extremely intolerant to the loss-of-function variation and hence mutations are extremely rare in the general population but enriched in individuals with neuropsychiatric disease (Koromina et al., 2019b). In addition to the genetic association, changes in KAR expression levels have been demonstrated in the brain tissue of patients diagnosed with psychiatric diseases (Beneyto et al., 2007). Rodent knockout or transgenic models have provided further evidence that dysfunction or gain-of-function of these receptors influences behavior in a manner that resembles endophenotypes associated with neurodevelopmental disorders (see Table 1). Pathophysiologically, role of KARs in neurodevelopmental disorders may arise from their involvement in broad spectrum developmental processes affecting maturation and function of behaviorally relevant neural circuitries. Although the causal link between developmental effects of KARs and aberrant behaviors remains to be established, recent findings in genetically modified mice have shed light on the possible KAR dependent mechanisms involved.

### Table 1

| Disorder/Phenotype | 1. Genetic association (SNPs, CNVs, susceptibility locus) | 2. Expression data from patient brain samples (mRNA, protein levels, receptor binding) | 3. Animal model (knock-out, overexpression, transgenic, drug induced) | References |
|--------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------|
| Schizophrenia      | Grik3, Grik4                                             | Grik1: decreased mRNA levels in perirhinal cortex; GluK1-3: decrease in numerical density of immunopositive neurons in orbitofrontal cortex | Grik1 KO: hyperactivity and impaired pre-pulse inhibition                  | Bengi et al. (2002); Garey et al. (2006); Pickard et al. (2006), 2008; Wilson et al. (2006); Beneyto et al. (2007); Lowry et al. (2014); Quednow et al. (2017); Koromina et al. (2019b) |
| Autism spectrum disorders | Grik1, Grik2, Grik3, Grik4, Netro1 | Grik2 KO: reduced sociability, loss of behavioral flexibility Grik4 KO: social impairment, enhanced anxiety, depressive states GluK1-5 KO: compulsive and perseverative behaviors | Grik2 KO: reduced sociability, loss of behavioral flexibility Grik4 KO: social impairment, enhanced anxiety, depressive states GluK1-5 KO: compulsive and perseverative behaviors | Grießwold et al. (2012); Micheau et al. (2014); Aller et al. (2015); Koromina et al. (2019b) |
| OCD                | Grik2                                                   | Grik1: decreased mRNA levels in perirhinal cortex                                     | Grik4 KO: antidepressant-like behavior                                    | Delorme et al. (2004); Mattheisen et al. (2015); Xu et al. (2017) |
| MDD                | Grik3                                                   | Grik1: decreased mRNA levels in perirhinal cortex                                     | Grik4 KO: reduced anxiety                                               | Beneyto et al. (2007); Schiffer et al. (2007); Catches et al. (2012); Smith et al. (2016) |
| Anxiety            |                                                        | Grik2 KO: hyperactivity, aggressiveness, symptoms responsive to lithium                | Grik4 KO: hyperactivity                                                  | Wu et al. (2007); Shaltiel et al. (2008); Catches et al. (2012); Masneuf et al. (2014); Aller et al. (2015) |
| Bipolar disorder   | Grik2, Grik3, Grik4, Grik5                             | Grik2: decreased mRNA levels in entorhinal cortex; Grik1: decreased mRNA levels in perirhinal cortex | Grik2 KO: hyperactivity, aggressiveness, symptoms responsive to lithium Grik4 KO: hyperactivity | Wilson et al. (2006); Beneyto et al. (2007); Shaltiel et al. (2008); Gratacós et al. (2009); Lowry et al. (2013) |
| Epilepsy           | Grik1                                                   | GluK1: protein upregulated in hippocampus                                             | Grik4 KO: reduced susceptibility to KA induced seizures; reduced discharges in animal model of TLE; GluK1 KO: reduced susceptibility to pilocarpine and ATPA (GluK1 agonist) induced seizures GluK1 OE (triplication in Ts2Cje mouse model of Down’s syndrome): impaired spatial memory | Mülle et al. (1998); Sander et al. (1997); Smolders et al. (2002); Rogawski et al. (2003); Eptiopin et al. (2005); Li et al. (2010); Fritsch et al. (2014); Perri et al. (2014); Valbuena et al. (2019) |
| Down syndrome      | Grik1 (chromosome 21)                                   |                                                                           |                                                                      |                                                                      |
| Cognitive impairment/intellectual disability | Grik1, Grik2, Grik3, Grik4 | Grik2 KO: loss of behavioral flexibility; impaired spatial learning |                                                                      |                                                                      |

References:

Delorme et al. (2004); Mattheisen et al. (2015); Xu et al. (2017); Beneyto et al. (2007); Schiffer et al. (2007); Catches et al. (2012); Smith et al. (2016); Wu et al. (2007); Shaltiel et al. (2008); Catches et al. (2012); Masneuf et al. (2014); Aller et al. (2015); Wilson et al. (2006); Beneyto et al. (2007); Shaltiel et al. (2008); Gratacós et al. (2009); Lowry et al. (2013); Mülle et al. (1998); Sander et al. (1997); Smolders et al. (2002); Rogawski et al. (2003); Eptiopin et al. (2005); Li et al. (2010); Fritsch et al. (2014); Perri et al. (2014); Valbuena et al. (2019).
intense synaptogenesis, but not later on in life, influence the strength of connectivity from LA to CeA (Ryzantseva et al., 2020). Specifically, loss of the developmental t-KAR activity results in altered excitability of late firing neurons in the CeA that are critically implicated in anxiety–like behaviors in mice (Tye et al., 2011; Cai et al., 2014). These results are consistent with the idea that developmental KAR malfunction, resulting in changes in the amygdala circuit function might be a causative factor in developmentally originating anxiety disorders (Fig. 5).

Impaired circuit development has also been characterized in the hippocampus of GluK2 deficient mice, where maturation of the behaviorally relevant mossy-fibre –CA3 synapse is significantly delayed (Marchal and Muller, 2004; Lanore, 2012). GluK2 deficient mice exhibit a variety of aberrant behaviors at the adult stage, including impaired spatial learning and memory (Mulle et al., 1998), social- and cognition-related behavioral phenotypes, altered locomotor activity, changes in anxiety-like behaviors, aggressiveness as well as increased sensitivity to psychostimulants, which resemble behavioral symptoms typical for autism (Micheau et al., 2014) and mania (Shaltiel et al., 2008). However, recent data indicates that there is a discrepancy in the phenotypes of GluK2 KO mice depending on their genetic background. GluK2 and GluK5 knockout mice with a pure C57BL/6J strain showed reduced locomotor activity and higher depressive-like behavior, but normal levels of anxiety and sociability (Tida et al., 2021). Since expression of GluK2 is critical not only for appropriate development of the mossy fibre synapses, but also for their adult functions, such as synaptic plasticity and integration (Mulle et al., 1998; Contractor et al., 2001; Sachidhanandam et al., 2005; Pinheiro et al., 2013), the precise contribution of the developmental vs. adult KAR functions to the behavioral phenotype in these mice remains to be established.

Interesting behavioral and neurophysiological phenotypes have been observed also in other mouse models with constitutive changes in KAR expression. Mice overexpressing GluK4 in the forebrain maintain the developmental tonic activity of the KARs until adulthood, and display significant changes in glutamatergic synaptic transmission in the amygdala (Arora et al., 2018) and in the hippocampus (Aller et al., 2015). Behavioral characterization of these mice revealed social impairment, enhanced anxiety and depressive states, common endophenotypes associated with autism spectrum disorders (Aller et al., 2015). On the other hand, ablation of GluK4 in mice results in anxiolytic and antidepressant phenotype as well as marked hyperactivity, which could be interpreted as an endophenotype for mania/hypomania of and antidepressant phenotype as well as marked hyperactivity, which could be interpreted as an endophenotype for mania/hypomania of bipolar phenotype in these mice remains to be established.

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