Kainate receptors and cognition enhancement

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Abstract

The kainate (KA) receptor family is one of the three ionotropic glutamate receptors (iGluRs) families, consisting of five subunits. The receptors were first discovered by the excitotoxic and epileptogenic actions upon kainate injection. The KA receptors are located on the nerve terminals as well as on the dendrites of neurons and induce ionotropic and metabotropic signalling pathways in areas like the hippocampus, amygdala, cerebellum and the cerebral cortex. Kainate receptors play a role in short-term and long-term synaptic facilitation and plasticity and are thereby a potential target for enhancing cognition. However, most of the actions of KA receptors are bidirectional and are highly dependent on experimental conditions, making them difficult subjects to study and target. This review describes some of the properties of these receptors and attempts to summarize the findings on cognitive modulation by KA receptors reported till now.

Key words: Kainate receptors, Glutamate, LTP, Cognition

Abbreviations used: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole proprionate; ATPA, (S)-2-amino-3-(5-tert-butyl-3-hydroxy-4-isoxazolyl)propionic acid; BLA, Basolateral amygdala; CAMs, Cell-adhesion molecules; CASK, Calmodulin-associated serine/threonine kinase; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; COPI, Coatomer protein complex I; eIPSC, Evoked IPSC; E-LTP, Eary LTP; EPSC/P, Excitatory postsynaptic current/potential; ER, Endoplasmic reticulum; GABA, Gamma-aminobutyric acid; GRIP, Glutamate-receptor-interacting protein; FF, Frequency facilitation; iGluRs, Ionotropic glutamate receptors; IPSP, Inhibitory postsynaptic potential; I_{sAHP}, slow afterhyperpolarization current; JNK, c-Jun terminal kinase; KA, Kainate; LFF, Low frequency facilitation; L-LTP, Late LTP; LTD, Long-term depression; LTP, Long-term potentiation; mGluRs, Metabotropic glutamate receptors; mRNA, Messenger ribonucleic acid ; NEM, N-ethylmaleimide; NMDA, *N*-methyl-D-aspartate; PDZ, Postsynaptic density-95/Discs large/zona occludens-1; PICK1, Protein interacting with protein kinase C; PKA, Protein kinase A; PKC, Protein kinase C; PLC, Phospholipase C; PPF, Paire-pulse facilitation; PSD, Post synaptic density; PTP, posttetanic potentiation; PTX, Pertussis toxin; SAPK, stress-activated protein kinase; SG, substantia gelantinosa; SLM, Stratum lacunosum moleculare; SO, Stratum oriens; SR, Stratum radiatum; TM, Transmembrane.

Contents

Introduction

The kainate (KA) receptor family is one of the three ionotropic glutamate receptors (iGluRs) families. Although a lot of research is done on the other two ionotropic glutamate receptor families, the NMDA and AMPA receptors, the function of KA receptors is less well established. This is mainly due to a lack specific pharmacological agonists and antagonists. Up to the discovery of a selective AMPA blocker in 1995, KA and AMPA receptor function couldn't be distinguished and were together referred to as non-NMDA receptor function (Paternain et al. 1995; Wilding et al. 1996; Huettner 2001). Studies were largely performed on dorsal root ganglion neurons since these express primarily KA receptors. Through the recent development of specific KA receptor subunit drugs and the generation of knockout mice more knowledge is gained about the specific functions of KA receptors. However, this knowledge is still largely based on only two of the five KA receptor subunits, GluK1 and -2 (Jane et al. 2009). Several properties now attributed to KA receptors are the regulation of neurotransmitter release (glutamate and GABA), control of neuronal excitability, and involvement in synaptic integration and plasticity (Pinheiro et al. 2006). KA receptors are abundant in the hippocampus and have shown to influence mossy fiber long-term potentiation (LTP) (Bortolotto et al. 1999; More et al. 2004). LTP, its opponent long-term depression (LTD), and synaptic plasticity are believed to be important processes for learning and memory.
Cognitive enhancers are drugs developed for healthy individuals who want to enhance their cognitive capacities, most importantly memory. The drugs tested till now are anti-dementia drugs which bind to NMDA receptors or acetylcholinesterase (Repantis et al. 2010). In addition nootropics, also known as 'smart drugs', have been used for enhancing cognition, but these are substances which effects are not (yet) scientifically proven. However, KA receptors play a significant role in the synaptic facilitation and plasticity and are thereby a potential target for enhancing cognition. The AMPA/KA antagonist CNQX has shown to induce retrograde amnesia (Bonini et al. 2003). In addition, selectively antagonizing the KA subunit GluK1 impairs recognition memory (Barker et al. 2006). Furthermore, in Alzheimer patients a reduction of KA receptors is shown in the hippocampus (Aronica et al. 1998).

Structure

KA receptors are transmembrane receptors consisting of four subunits. Each subunit consists of three transmembrane domains and one loop within the membrane. This re-entrant membrane loop lines the inner channel pore and is important for defining the ion selectivity (Bigge 1999). The subunits are called GluK1-GluK5 according to the new nomenclature suggested by NC-IUPHAR, but are also known as GluR5, GluR6, GluR7, KA1 and KA2 (see table 1) (Collingridge et al. 2009). The subunits form a pore which opens upon binding of the endogenous ligand glutamate or exogenous ligands, like KA and domoate acid, and through which cations may pass (Pinheiro et al. 2006). The GluK1-3 subunits are low affinity subunits and show affinity for KA in the range of 50-100nM (Egebjerg et al. 1991; Bettler et al. 1992; Sommer et al. 1992; Schiffer et al. 1997). GluK4 an -5 are on the other hand high affinity subunits and show affinity for KA in the range of 5-15nM (Werner et al. 1991; Herb et al. 1992). The EC_{50} for glutamate is in the range of 8-50μM for GluK1 and GluK2 homomeric and heteromeric assemblies with GluK5, while for GluK3 this value is ~6mM (Schiffer et al. 1997; Alt et al. 2004). GluK1 homomeric and GluK2 and -3 heteromeric receptors combined with GluK4 or -5 are also able to bind AMPA. GluK2 and -3

homomeric receptors are however insensitive to AMPA (Egebjerg et al. 1991; Lerma 1997; Schiffer et al. 1997).

In addition to the five different subunits, GluK1-3 have multiple splice variants and variation occurs through RNA editing. The sequences of the splice variants differ mostly in the cytoplasmic C-terminus, creating four splice variants for GluK1 and three for GluK2 and two for GluK3 each, designated a till d (Gregor et al. 1993a; Schiffer et al. 1997; Jamain et al. 2002). GluK1 also has alternative splicing variant which differs in the N-terminus, called GluK1-1 and GluK1-2 (see Fig. 1). The alternative splicing impacts the intracellular trafficking, the regulatory processes and the interacting partners. There are no splice variants discovered for GluK4 an -5.

Table 1: New NC-IUPHAR nomenclature and previous nomenclature of ionotropic glutamate receptor subunits

New nomenclature (NC-IUPHAR)	Old nomenclature	Human gene names
GluK1	$GluK_5$, GluR5, GluR-5, EAA3	GRIK1
GluK2	$GluK_6$, GluR6, GluR-6, EAA4	GRIK2
GluK3	$GluK_7$, GluR7, GluR-7, EAA5	GRIK3
GluK4	Glu_{K1}, KA1, KA-1, EAA1	GRIK4
GluK5	Glu_{K2}, KA2, KA-2, EAA2	GRIK5

GluK1 and -2 can be post-transcriptional nuclear edited at the so-called Q/R site which influences their permeation for Ca^{2+} ions (Sommer et al. 1991; Kohler et al. 1993). The Q/R site is located in the second membrane site (TMII or MII) and during editing the nucleotide glutamine (Q) is exchanged for an arginine (R) (Sommer et al. 1991). The GluK2 subunit has two additional editing sites in the first transmembrane (TM1) loop, named I/V and Y/C (Kohler et al. 1993). The editing is developmentally and regionally regulated (Bernard et al. 1994; Bernard et al. 1999). In adult rat brain 40-55% and 80-90% of the GluK1 and GluK2 receptors are edited (Sommer et al. 1991; Bernard et al. 1999). The editing has consequences for receptor functioning. Unedited GluK2 has a low Ca^{2+} permeability, whereas editing the Q/R site increases the permeability (Kohler et al. 1993), although the opposite is also suggested (Egebjerg et al. 1993). Although editing of the TM1 does not have a large effect in the GluK2 (R) subunit, it does decrease permeability in the GluK2 (Q) subunit. Editing the GluK1 and -2 subunits may be a way of the cell to regulate the glutamate-induced Ca^{2+} influx.

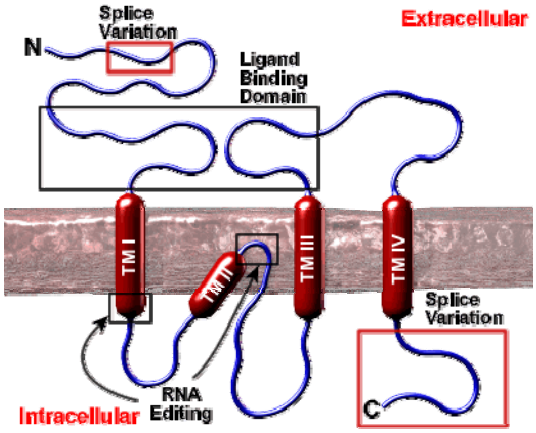

Fig. 1: Structure of the KA receptors. There are three transmembrane domains and one loop within the membrane. Splice variance at the cytoplasmic C-terminus is reported for GluK1, -2 and -3, whereas splice variation in the N-terminus is only seen in GluK1. The RNA editing site at the TMII is called the Q/R site and present in GluK1 and -2. The RNA editing site in the TMI has been shown in GluK2 (MRC Centre for Synaptic Plasticity 2010).

The GluK1, -2 and -3 subunits can form homomeric channels, but are also able to combine with other subunits (Schiffer et al. 1997; Cui et al. 1999). The subunits GluK4 and -5 are not able to form homomeric channels and have to combine with GluK1-3 to form a functional heteromeric channel (Werner et al. 1991; Herb et al. 1992; Gallyas et al. 2003). Although KA and AMPA receptors share many

common features, their subunits are not able to co-assembly. The formation of these heteromeric assemblies modifies the properties and biophysical function of the receptor, as will be discussed further on in this review.

Expression

The KA receptor subunits are differentially expressed in the brain (see Fig. 2). KA receptors show overlap with AMPA receptor expression in some brain areas and synapses. All subunits are expressed in the hippocampus, which is thought to be important in spatial and long-term memory. The hippocampus is the most studied area for determining the function of KA receptors.
GluK2 and –5 are the most widely expressed subunits of the KA receptor (see also in the Supplementary); especially GluK5 is ubiquitously expressed (Herb et al. 1992; Wisden et al. 1993). GluK5 protein expression is highly dependent on the expression of the GluK2 subunit, while reports on the necessity of GuK1 for GluK5 subunit expression are inconsistent (Christensen et al. 2004; Ruiz et al. 2005; Ball et al. 2010). On the other hand, GluK2/3 localization at the mossy fiber-CA3 synapses is dependent on GluK4/5 expression (Fernandes et al. 2009). In contrast to the other subunits, GluK4 expression is very limited and well-defined with its highest expression in the CA3 region of the hippocampus (Werner et al. 1991; Bahn et al. 1994).
The expression of KA receptors is developmentally regulated. KA receptors are downregulated over the development and seem to be activity-dependent replaced by AMPA receptors (Kidd et al. 1999; Hirbec et al. 2005).

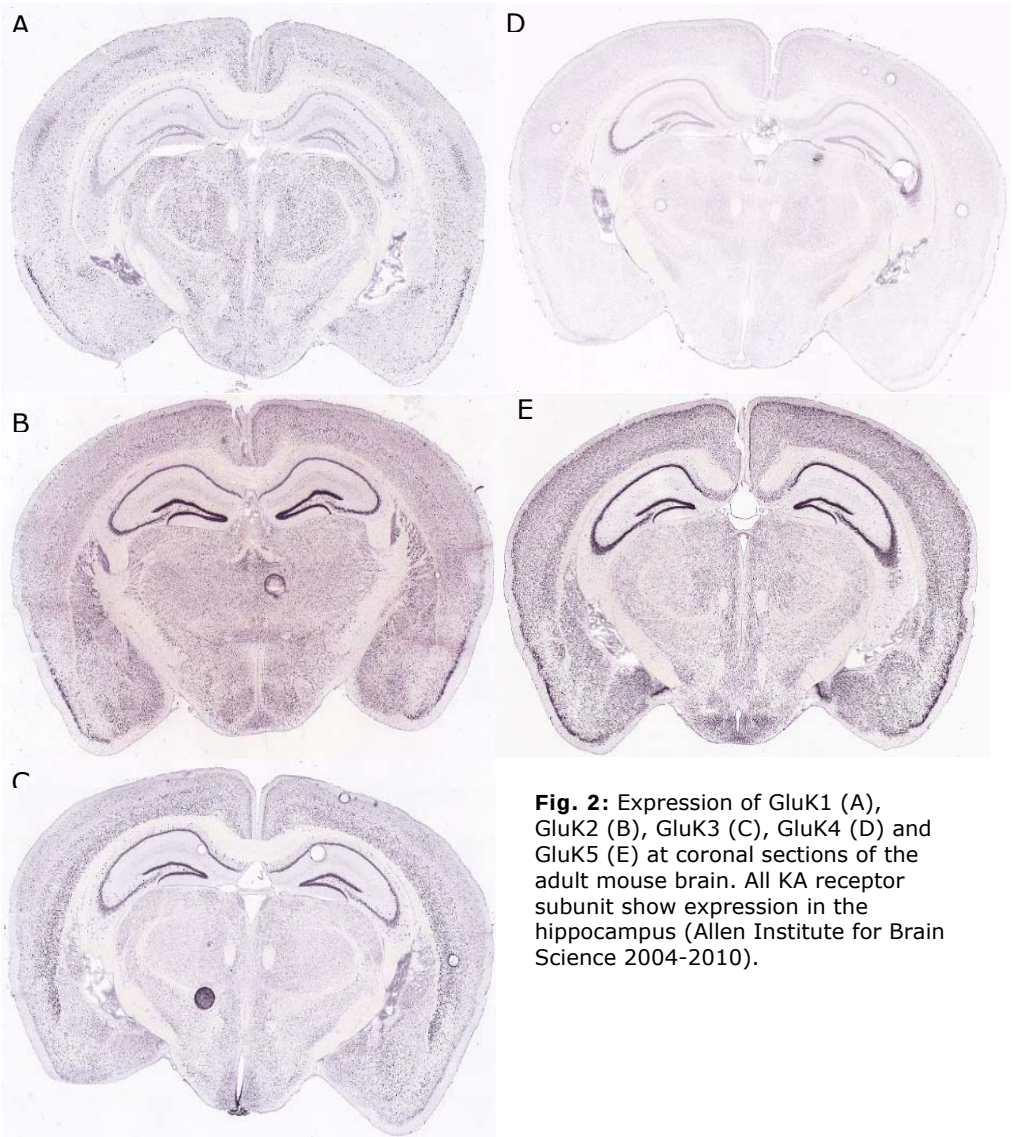

Fig. 2: Expression of GluK1 (A), GluK2 (B), GluK3 (C), GluK4 (D) and GluK5 (E) at coronal sections of the adult mouse brain. All KA receptor subunit show expression in the hippocampus (Allen Institute for Brain Science 2004-2010).

Synaptic function

The study for the function of KA receptors has been hampered by the lack of selective ligands for the different KA subunits and even selective for KA receptors over all. KA receptors were believed for a long time to mediate the excitotoxic and epileptogenic actions of the exogenous ligand KA (Lerma 1997). However, KA is also able to bind to the AMPA receptor family. Given that AMPA receptors are present in the same areas as KA receptors and have a higher peak amplitude than KA receptors after activation (Frerking et al. 2000), it is plausible that (the biggest) part of the effects of KA are due to AMPA receptor activation. Nevertheless, KA receptors are still thought to play an important role in these actions. However, additional actions of the receptors, including involvement in cognition, are now being considered.
KA receptors are located both at dendrites and nerve terminals and on both glutamatergic and GABAergic neurons. At the nerve terminals KA receptors can function both as autoreceptor and heteroreceptor. Furthermore, as will be shown later on in this chapter, KA receptors seem to have both ionotropic and metabotropic actions.

Biophysical properties
KA receptors display a bidirectional effect: low concentrations of KA enhance glutamate release and mossy fiber EPSC while higher concentrations depress glutamate release and mossy fiber transmission (see also Fig. 3) (Schmitz et al. 2001a; Schmitz et al. 2001b). The duration of neurotransmitter release or postsynaptic depolarization after KA receptor activation is strongly dependent on desensitization kinetics. The time of activation and the desensitization kinetics differs per agonist, concentration of the agonist and per subunit composition (Swanson et al. 1997), and may therefore differ in animal age and per area.

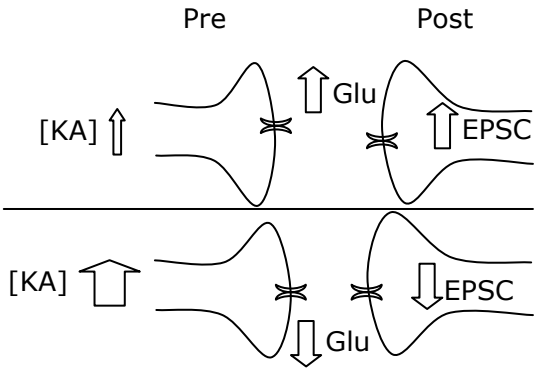

Fig. 3: Bidirectional effect of KA receptors. Low concentrations of KA increase the glutamate release from the nerve terminal and increases the EPSCs, while high concentrations of KA decreases glutamate release and the EPSCs.

Homomeric GluK1 receptors show a slow desensitization after domoate binding, but a more rapid, dual-exponential desensitization occurs after KA application (Sommer et al. 1992). Desensitization is (almost) complete after glutamate binding in HEK293 cells and dorsal root ganglion (DRG) neurons, depending on the concentration (Huettner 1990; Sommer et al. 1992). Assembly of GluK1(Q) with the GluK5 subunit causes more rapid desensitization kinetics compared to homomeric GluK1(Q) (Herb et al. 1992).
Homomeric GluK2 channels have fast desensitization kinetics and show a slow recovery (Egebjerg et al. 1991; Lerma et al. 1993). Although long or high application of glutamate shows equal kinetics for homomeric GluK2 and heteromeric GluK2/5 receptors, short or low application causes a slower desensitization of GluK2/5 (Barberis et al. 2008). A faster recovery from desensitization from dysiherbaine (a subtype-selective agonist for ionotropic glutamate receptors) occurs if GluK5 is co-expressed with GluK2, but this is not the case for recovery from glutamate (Swanson et al. 2002; Barberis et al. 2008). For GluK2/4 the recovery is also similar to that from homomeric GluK2 (Mott et al. 2010). Co-expression of GluK4 with GluK2 also causes a lower desensitization, suggesting that the high-affinity GluK4 and -5 subunits are relatively non-desensitizing. Furthermore, knocking out the GluK5 subunit increases ESPC decay in mossy fibers (Sachidhanandam et al. 2009).

GluK3 also shows rapid and almost complete desensitization to glutamate and KA, both as homomeric and heteromeric channels in combination with GluK4 or -5 (Schiffer et al. 1997). This desensitization is faster at subsaturating concentration of glutamate than at saturating concentrations (Perrais et al. 2009a). GluK3 was long thought to be unable to form functional homomeric channels, because no GluK3-induced current could be detected due to its high desensitization.

KA receptors show a rapid activation and desensitization upon KA-induced activation in embryonic hippocampal neurons (Lerma et al. 1993), but slow and incomplete desensitization has been reported in postnatal rat hippocampal neurons (Wilding et al. 1997; Kidd et al. 1999). This difference may be caused by an increase in GluK1 subunits in the hippocampus shortly after birth, which is the same age as the animals used in the postnatal study (Bahn et al. 1994; Wilding et al. 1997; Kidd et al. 1999). The low decay kinetics and slow desensitization currents of the receptors in mossy fibers (Castillo et al. 1997) may as well be caused by the GluK1 subunit, but might also be mediated by the GluK2/5 heteromeric receptors with slower desensitization. The slow desensitization causes relatively long-lasting depolarization in the postsynaptic neuron, which can play a role in postsynaptic summation. This summation leads to enhancement of the amount of axon potentials and may potentiate synaptic transmission.

Besides to intrinsic differences between the receptor subunits, interacting proteins are also able to change the biophysical properties of the receptors. A number of transmembrane accessory proteins are able to bind to AMPA receptors and thereby affect their trafficking and change kinetic and channel properties (Diaz 2010). There are also two transmembrane accessory proteins known which are able to bind to KA receptors, known as NETO2 and NETO2 (Zhang et al. 2009). Although NETO2 also modulates channel properties, it has no affect on KA receptor trafficking. Binding of NETO2 to GluK2 prolongs glutamate-induced currents, modulates agonist sensitivity, increases the receptor open probability peak and thereby increases peak amplitude. The absence of NETO2 in the CA1 hippocampal interneurons might underlie the shorter $EPSC_{KA}$ decay times in this area (Zhang et al. 2009) and maybe less involvement in the synaptic transmission here. KA receptors may therefore be more important in the LTP induction in the CA3 area compared to the CA1 area, where the NMDA receptors are known to induce LTP.

Presynaptic autoreceptors

Presynaptic autoreceptors are facilitatory or inhibitory receptors, modulating glutamatergic neurotransmitter release in a bidirectional manner. Low concentrations of KA increase the release of glutamate, while high concentrations depress the release (Chittajallu et al. 1996; Contractor et al. 2000; Lauri et al. 2001a; Schmitz et al. 2001b). They mediate forms of short-term plasticity (STP), like frequency facilitation (FF) and paire-pulse facilitation (PPF), but are also involved in LTP at mossy fiber synapses (Contractor et al. 2000; Contractor et al. 2001; Breustedt et al. 2004). STP is a form of synaptic plasticity which lasts only for a few seconds. PPF is the increase in synaptic response size when a synapse is activated twice at short intervals (Mulle et al. 1998) lasting about 20-40s (Salin et al. 1996), while FF is an increase of synaptic facilitation induced by sustained elevated frequency stimulation (Fernandes et al. 2009). KA autoreceptors are thought to be involved in the mossy fiber-CA3 synapses sensing glutamate release and consequently increasing (or decreasing) glutamate release, thereby enhancing short-term synaptic plasticity (Contractor et al. 2001; Schmitz et al. 2001b). At the synapses between the Schaffer collateral-commissural terminals and CA1 neurons KA autoreceptors have a biphasic action. Initially they enhance the glutamate release and thereby the NMDA receptor-mediated EPSCs, followed by a depression of release and EPSCs (Chittajallu et al. 1996).

The autoreceptors may induce the synaptic facilitation through either depolarization of the presynaptic membrane and/or increasing the Ca^{2+} influx (Schmitz et al. 2003). Ca^{2+} permeability seems to be necessary for these functions, since blocking calcium-permeable glutamate receptors with philanthotoxin-433 reduces the PPF and FF (Perrais et al. 2009b). Intracellular Ca^{2+} release is suggested to contribute to presynaptic KA receptor function (Lauri et al. 2003). Furthermore, inhibition of glutamate release by high concentrations of KA is thought to be primarily a consequence of a reduction in Ca^{2+} (Kamiya et al. 1998; Kamiya et al. 2000). However, as addition of 4mM K^+ is able to mimic the effects of KA on mossy fibers, it is also probable that the facilitation of KA receptors is mediated by a depolarizing action on the nerve terminal (Schmitz et al. 2001b).

The presynaptic autoreceptors at the mossy fiber synapses probably exist of GluK2 and -3 subunits. GluK3 is expressed at substantial levels in the dentate gyrus. However, GluK3 receptors have low glutamate sensitivity and are therefore not easily activated (Perrais et al. 2009a). It is therefore suggested that GluK3 subunits are located near glutamate release sites. They will be activated only when the mossy fiber nerve terminals have a hyperpolarized resting potential, because of a spermine block (see Trafficking) which is only released close to resting potential (Perrais et al. 2009a). The hyperpolarization will occur after an action potential has occurred and glutamate is released from the nerve terminal, creating high glutamate levels near the GluK3 receptors. GluK3 receptors would act as low-pass / high-threshold filters for the discrimination of strength of the excitatory synaptic input, because of the high glutamate concentration needed at low-frequency to activate the receptor (Schiffer et al. 1997; Perrais et al. 2009a). Presynaptic autoreceptors at mossy fiber synapses consist of heteromeric co-assemblies of GluK3 with GluK2 subunits located at the active zone of the presynaptic terminal close to the glutamate release sites (see Fig. 4) (Pinheiro et al. 2005; Perrais et al. 2009b). Antagonists UBP302, UPB310 and UBP316 are able to block homomeric, but not heteromeric GluK3 receptors and do not affect presynaptic KA receptors at mossy fiber synapses (Perrais et al. 2009b). Furthermore, the KA receptors induce PPF at short interstimulus intervals at the mossy fiber synapses, which is impaired in both GluK2 and -3 knock out mice (Contractor et al. 2001; Pinheiro et al. 2007). FF was also reduced in GluK2 and -3 deficient mice, whereas GluK1 deficiency does not lead to alterations in STP (Contractor et al. 2001; Pinheiro et al. 2007). These actions occur rapidly, concluding that these are ionotropic actions of KA receptors and no G-protein-coupled process is involved in this function. Moreover, synaptic facilitation is not influenced by an inhibitor of the metabotropic action of KA (protein kinase C inhibitor calphostin C) (Rodriguez-Moreno et al. 1998). The presynaptic receptors are also thought to be involved in LTP, although they are not thought to be essential (Lauri et al. 2001a; Schmitz et al. 2003).
The involvement of GluK1 subunits in presynaptic autoreceptor function at mossy fibers is also suggested. The GluK1 selective antagonist LY382884 reduces the mossy fiber FF and presynaptic induced LTP in some studies (Bortolotto et al. 1999; Lauri et al. 2001a; Lauri et al. 2001b), but does not have that effect in all studies (Breustedt et al. 2004). However, GluK1 deficiency does not abolish KA-induced synaptic facilitation (Contractor et al. 2001; Breustedt et al. 2004) and GluK1 mRNA is not or barely detected in DG cells (Wisden et al. 1993; Bahn et al. 1994; Bureau et al. 1999), making GluK1 as presynaptic autoreceptor in mossy fibers less probable. An explanation for this could be that there are heteroreceptors which do or do not contain the GluK1 subunit present on the mossy fiber terminals, which are also responsive to the GluK1 antagonists. However, LY382884 has shown to reduce synaptic facilitation in wild-type mice, but not in $GluK1^{-/-}$ mice (Bortolotto et al. 2003), suggesting that the GluK1 subunit must be present for exerting its actions. This would leave out the possibility of less selective inhibition of homo- or heteroreceptors without the

GluK1 subunit. Secondly, in the absence of GluK2, GluK1 may not be able to form functional homomeric receptors or may not be transported to the correct subcellular localization, while GluK2 is able to function without GluK1. A third possibility is that the GluK1 antagonists affect mossy fiber currents via an indirect mechanism, for instance via GABAergic interneurons which do contain the GluK1 subunit (see also Pre- and postsynaptic heteroreceptors) (Bureau et al. 1999; Huettner 2001), like shown for the GluK1 agonist ATPA (Schmitz et al. 2000). GluK4 and -5 localization is also shown at presynaptic mossy fiber boutons and in dendritic spines (Darstein et al. 2003). GluK5 is however mostly expressed postsynaptic, both at the synapse as extrasynaptically (Darstein et al. 2003) and deficiency of GluK5 does not influence homosynaptic glutamate release (Contractor et al. 2003).

Unlike at the mossy fiber and parallel fiber synapses, presynaptic KA autoreceptors located at the CA3 - CA1 pyramidal cell synapses (see Fig. 3b) are thought to act via a direct metabotropic action (Frerking et al. 2001). The G_i/G_o G-protein subtypes are suggested to be involved in the depression of glutamate release via the inhibition of Ca^{2+} channels (Frerking et al. 2001). These autoreceptors probably also involve the GluK2 subunits, since GluK2-selective antagonist NS-102 is able to inhibit the presynaptic effects of KA (Chittajallu et al. 1996).

Pre- and postsynaptic heteroreceptors
Heteroreceptors are receptors that are activated by their neurotransmitter released from another neuron or synapse than were they are located themselves. Heterosynaptic regulation of glutamate occurs at both glutamatergic and GABAergic synapses. Activation of the receptors by glutamate in mossy fibers leads to either synaptic inhibition or facilitation, depended on the tetanus duration (Schmitz et al. 2000; Schmitz et al. 2001a). Heterosynaptic regulation is thought to depend on GluK2 and -5 subunit containing receptors, contrary to the composition of autoreceptors (Contractor et al. 2003; Pinheiro et al. 2006). GluK5 deficiency leads to absence of hetero-synaptic facilitation of mossy fiber EPSCs (Contractor et al. 2003). It is not clear where these receptors are exactly located. Unlike the autoreceptors these receptors may be located further away from the glutamate release sites. Antidromic mossy fibers spikes are reported to be induced by a glutamate spill over from glutamate release at commissural/ associational synapses (Uchida et al. 2010), confirming heteroreceptor activation.

Besides influencing glutamate release and transmission, KA heteroreceptors have shown to regulate GABA release, modulating GABA-induced inhibitory postsynaptic currents (IPSC). The modulation of GABA release by KA receptors might be regulated by receptors located on the GABAergic terminals themselves, but may also be located on the somatodendrites. The modulation of GABA transmission by KA is thought to be crucial in the onset of epileptiform activity and modulation of neuronal excitability (Fisher et al. 1984; Avoli et al. 1996; Uva et al. 2009).
There is a biphasic effect or bell-shaped curve of KA in the hippocampus on evoked IPSCs (eIPSCs) (Rodriguez-Moreno et al. 1997; Kerchner et al. 2001), with no effect on eIPSCs with low doses (and extremely high doses) and a suppression of IPSC amplitude by high doses of KA between interneuron-CA1 pyramidal cell connections, leading to synaptic disinhibition (Clarke et al. 1997; Rodriguez-Moreno et al. 1997; Rodriguez-Moreno et al. 1998; Kerchner et al. 2001; Maingret et al. 2005). On the other hand, application of KA has also shown to be able to increase the frequency of miniature, unitary and spontaneous IPSCs (Cossart et al. 1998; Bureau et al. 1999; Mulle et al. 2000; Cossart et al. 2001; Jiang et al. 2001; Christensen et al. 2004). Cossart et al. did not find a difference in amplitude and increase in GABA release in both studies, but this could be due

to a high Mg^{2+} concentration. Raising the Ca^{2+} and Mg^{2+} concentrations leads a shift in the biphasic effect, having a facilitation effect at low concentration and keeping the suppression effect at high concentrations (Kerchner et al. 2001). Another theory is that presynaptic KA receptors enhancement of the GABA/glycine release between interneurons may subsequently lead to suppression of GABA release by presynaptic $GABA_B$ autoreceptor activation (Frerking et al. 1999; Kerchner et al. 2001). However, another study reported there was no involvement of $GABA_B$ receptors in reducing evoked IPSCs in the CA1, as shown by antagonising of these receptors (Clarke et al. 1997). Because of the contrary results, the exact function and mechanism of KA receptors on GABAergic neurons is not yet clear.

The KA heteroreceptors on GABAergic interneurons probably consist of heteromeric assemblies of GluK1 and GluK2 subunits (Mulle et al. 2000; Paternain et al. 2000). GluK1 is highly expressed in GABAergic interneurons in the stratum radiatum (SR) and oriens (SO) (Bureau et al. 1999) and effects of KA are mimicked by GluK1 agonist ATPA, but inhibited by GluK1 antagonists LY293558 (Cossart et al. 1998) and LY382884 (Christensen et al. 2004). LY382884 was ineffective in GluK1 knock out mice, showing the requisite of this subunit. Interestingly, the homomeric GluK1 antagonist NS3763 did not have an effect at all (Christensen et al. 2004), suggesting heteromeric assemblies containing the GluK1 subunit must be involved. In support of this conclusion, the reduction of GABA release by KA is not abolished by only knocking out GluK1 or GluK2, but is completely lost in $GluK1^{-/-}$x$GluK2^{-/-}$ mice (Bureau et al. 1999; Mulle et al. 2000). On the other hand, enhancement in the release of GABA between interneurons (Mulle et al. 2000; Lerma 2003), increases in spontaneous IPSC amplitude and frequency and decreases in eIPSC (Fisahn et al. 2004) are absent in GluK2 knock out mice, suggesting no key role for GluK1 in these processes. This indicates that the bidirectional effect may be regulated by receptors with a different subunit composition.
The heteroreceptor function of the KA receptors at the CA1 pyramidal cells is thought to rely on metabotropic actions. KA receptor activation leads to the stimulation of phospholipase C (PLC) and protein kinase C (PKC) (see Fig. 3a), which results in the inhibition of GABA release (Rodriguez-Moreno et al. 1998). Furthermore, the ion flux through the KA receptors does not seem to influence the GABA induced IPSCs (Rodriguez-Moreno et al. 1997) and facilitation of GABA release at low concentrations is not sensitive to a Ca^{2+} channel block (Cossart et al. 2001). However, the depolarizing action of KA was not sensitive to inhibition of PKC or G-proteins, suggesting two populations of KA receptors in the hippocampal interneurons (Rodriguez-Moreno et al. 2000), making interpretations of the experiments more difficult. These different populations may have different compositions, localization, agonist sensitivity and signalling mechanisms. Receptors on the presynaptic site regulating GABA release have a greater sensitivity glutamate than postsynaptic receptors regulating the depolarization (Rodriguez-Moreno et al. 2000), suggesting a difference in subunit composition or localization closer to the glutamate release site. The presynaptic heteroreceptor will activate a metabotropic pathway depending on PKC, while the postsynaptic heteroreceptors will exert an ionotropic function.

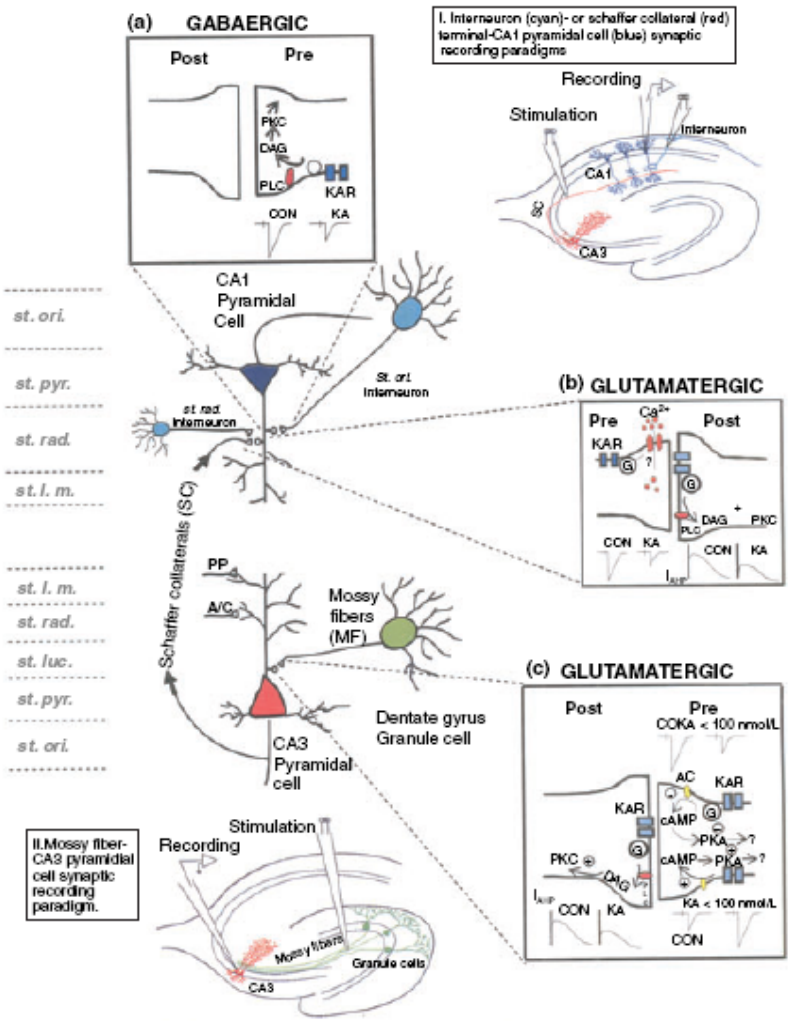

Fig. 3: Locations and proposed signalling pathways induced by KA receptors in the hippocampus. KA receptors are present at the mossy fiber-CA3 synapses (c), CA3-CA1 synapses (b) and on GABAergic interneurons (a). In addition, KA receptors are present extrasynaptically on nerve terminals. Beside the ionotropic actions of the receptors, they also exert metabotropic actions which involve either PKC or PKA. In the enlarged pictures evoked post-synaptic currents are shown in control conditions (CON) and in the presence of kainate (KA). Activation of presynaptic KA receptors reduce the EPSCs at concentrations higher than 100nmol/L, while presynaptic activity after less than 100nmol/L KA or the activation of postsynaptic KA receptors enhance the EPSCs (Rodriguez-Moreno et al. 2007).

Bidirectional modulation of GABA release by KA receptors has also been reported in the amygdala (Braga et al. 2003). GluK1-containing KA receptors are thought to be located on the presynaptic terminals of GABAergic neurons and on postsynaptic membranes of interneurons and pyramidal neurons in the basolateral amygdala (BLA) (Braga et al. 2003; Braga et al. 2004). The effects of glutamate on IPSCs in the amygdala can be mimicked by GluK1-'selective' ATPA and inhibited by LY293558.

Postsynaptic receptors

Postsynaptic KA receptors contribute to excitatory postsynaptic currents and potentials (EPSC/P) after glutamate activation. The EPSCs generated at some synapses by KA are dual-component EPSCs, consisting of an AMPA receptor-mediated current and a KA receptor-mediated current. Postsynaptic KA receptor activation was first shown in mossy fibres in the pyramidal cells of the CA3 region of the hippocampus (Castillo et al. 1997; Vignes et al. 1997). Contribution to the EPSP has later on also been reported in other parts of the hippocampus, the retina, amygdala, spinal cord and cortex. The amplitude, rise and decay kinetics of the EPSC of KA receptors is much lower and slower than of AMPA receptors, although the values may differ per area. For example, the kinetics for both receptors is faster in CA1 interneurons than in the CA3 pyramidal cells (Cossart et al. 2002). KA receptors are also able to depress the EPSC in mossy fibers and collateral synapses (Kamiya et al. 1998; Bortolotto et al. 1999; Contractor et al. 2000).

The EPSC were first believed to be generated mainly or entirely by receptors containing the GluK1 subunit. Different GluK1-selective antagonists showed to reduce the amplitude of KA receptor-induced EPSCs in CA3 neurons. KA receptors in the somatodendritic site of interneurons in the SR and stratum lacunosum moleculare (SLM) do not contain the GluK1 subunit. However, GluK1 is present in the postsynaptic site of these cells, suggesting a role in the modulation of the EPSC. There are no GluK1 receptors found in the interneurons of the stratum oriens (SO) in one study (Wondolowski et al. 2009), but highly expressed in the SO (and SR) in another study (Bureau et al. 1999). So also for this function, the exact location and importance of the GluK1 subunit in generating the EPSCs is still unclear. GluK2 knock out studies showed an important role for this subunit in KA receptor-mediated EPSCs at CA3 neurons and CA1 pyramidal cells (Mulle et al. 1998; Bureau et al. 1999).
Although most of the functions of KA channels are assigned to GluK1 and -2, the high affinity KA receptors also play an important role. GluK2/GluK5 predominant form of postsynaptic KA receptors (see Fig. 4) (Petralia et al. 1994). The slow deactivation currents mediated by GluK2/5 receptors are similar to the time course of reported KAR-EPSCs, indicating postsynaptic receptors consist of GluK2/5 heteromeric receptors (Barberis et al. 2008). However, it is shown that in GluK5 knock out mice the EPSCs show faster decay rate (Contractor et al. 2003), but still markedly slower as GluK2 homomeric receptors mediate. It is suggested that GluK4, which is abundantly expressed in the CA3 region but mostly on nerve terminals (Darstein et al. 2003), might be able to replace GluK5 as developmental compensation mechanism (Barberis et al. 2008). Disruption of the Grik4 gene leads to a significant decrease in synaptic KA receptor-mediated currents. Knocking out both GluK4 and -5 subunits causes a complete loss of the synaptic function and EPSCs of KA receptors in the hippocampal mossy fibers (Fernandes et al. 2009).

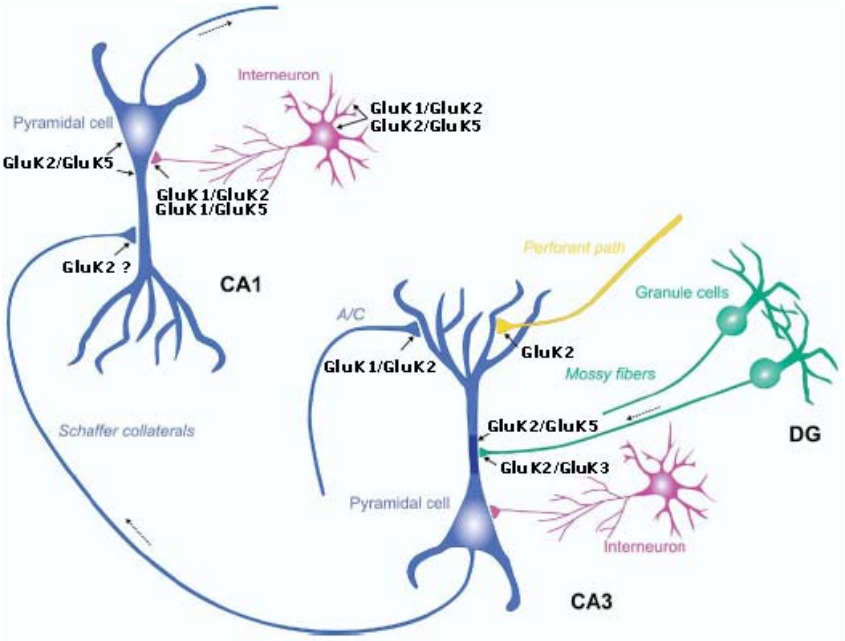

Fig. 4: Some of the proposed KA receptor subunit compositions at the hippocampal synapses. The GluK3 subunit is thought to be only present on nerve terminals, while GluK2 and GluK5 are present on nerve terminals and dendrites. The GluK1 subunit is also present on nerve terminals, but its present on dendrites is still an issue of discussion. The GluK4 subunit is the least widely expressed and least studied subunit and it is therefore not precisely known where it exerts its function. Picture adjusted from (Vincent et al. 2009)

It was also first believed that there were extrasynaptic KA receptors mediating EPSPs. This was thought because of the slow kinetics, the slow EPSC of the KA receptors, which would be generated by glutamate spillover. However, blocking the spillover or glutamate uptake does not change the slow kinetics of KA receptors (Castillo et al. 1997; Bureau et al. 2000; Kidd et al. 2001), and quantal release of glutamate also activates KA receptors, suggesting an intrinsic property

of the receptors (Cossart et al. 2002; Wondolowski et al. 2009). Although the KA receptors are thus present at the synapse itself and are directly involved in the synaptic transmission, extrasynaptic KA receptors are also present in somadendritic compartments of CA1 pyramidal cells and neocortical layer V neurons, probably executing metabotropic effects of KA receptors (Eder et al. 2003).

Metabotropic actions

Although KA receptors are ion channels, there is evidence that they also execute metabotropic actions as already discussed above. It is thought that the ionotropic and metabotropic actions of KA receptors are independent processes processed by the same receptor (Rozas et al. 2003; Rivera et al. 2007). Besides the metabotropic role in GABA and glutamate release at the CA1 synapses (Rodriguez-Moreno et al. 1998; Frerking et al. 2001), the metabotropic actions of KA receptors are thought to be responsible for the inhibition of postspike slow and medium afterhyperpolarization (AHP) currents (I_{sAHP} and I_{mAHP}) in CA3 pyramidal neurons (Fisahn et al. 2005) and inhibition of I_{sAHP} in CA1 pyramidal neurons (Melyan et al. 2002; Melyan et al. 2004). The I_{sAHP} and I_{mAHP} are voltage-independent, Ca^{2+} dependent K^+ currents, which are induced after short bursts of action potentials (see Fig. 5) (Lancaster et al. 1986). The duration of the current is up to several seconds, proportionally to the frequency and number of action potentials. By this mechanism a negative feedback loop is activated, which limits burst firing and repetitive spiking during hyperexcitability (Madison et al. 1984; Traub et al. 1993; Melyan et al. 2002). KA receptors inhibit the I_{sAHP}, thereby increasing the neuronal excitability for several seconds (Melyan et al. 2002; Sachidhanandam et al. 2009).

The modulation of glutamate release at the Schaffer collateral-CA1 pyramidal cell synapses is blocked by inhibition of G-proteins (by Pertussis toxin (PTX) and N-ethylmaleimide (NEM)), but not by a broad spectrum protein kinase inhibitor (Frerking et al. 2001). It is proposed that the G-protein involved directly inhibits presynaptic Ca^{2+} channels, thereby depressing the release of glutamate. A second alternative may involve a second messenger system which is kinase-independent (Rodriguez-Moreno et al. 2007).

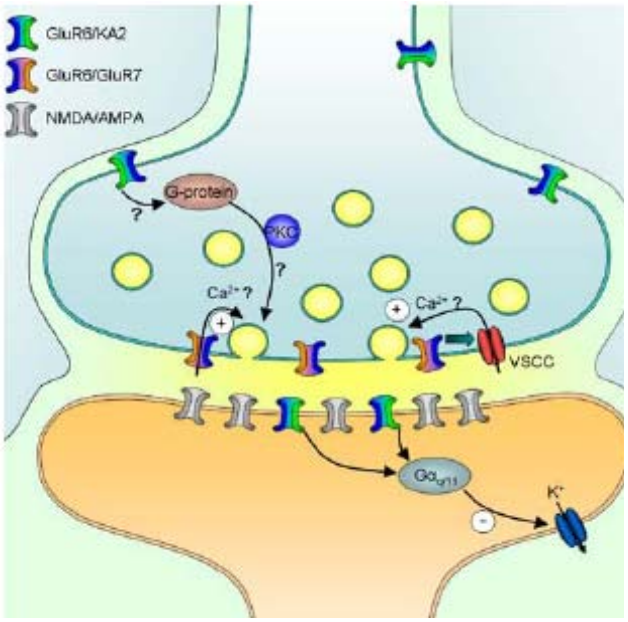

Fig. 5: Schematic and hypothetical representation of the mechanisms of action of presynaptic and postsynaptic kainate receptors (PKC protein kinase C, VSCC voltage-gated Ca2+ channels) at the mossy fibre synapse. Presynaptic kainate receptors acting as autoreceptors are probably localized close to the synaptic release site where they function as fast facilitatory receptors, either by a direct influx of Ca2+ through the kainate-receptor channel or through depolarization of the presynaptic membrane. Heterosynaptic kainate receptors are thought to be localized at some distance from the neurotransmitter release site, are activated by the diffusion of glutamate from its source and act with a slower time course to facilitate or depress synaptic transmission. Activation of postsynaptic kainate receptors (1) generates an EPSC with integrative properties that leads to the cumulative depolarization of the postsynaptic membrane and (2) induces a down-regulation of the slow IAHP, leading to an increase in neuronal excitability. These various actions are proposed to arise from kainate receptors with distinct subunit compositions. (Pinheiro et al. 2006)

The metabotropic actions on GABA release are blocked by PTX and NEM, by inhibition of phospholipase C (PLC) (by U73122) and PKC (by calphostin C)

(Rodriguez-Moreno et al. 1998; Cunha et al. 2000), but not by a PKA inhibitor (Rodriguez-Moreno et al. 1998). This suggests that KA receptors exert metabotropic actions on neurotransmitter release by activating G-proteins, PLC and PKC subsequently. PKC is also the essential protein kinase in the KA-induced I_{sAHP} and I_{mAHP} in CA3 pyramidal cells (Fisahn et al. 2005).
The metabotropic actions of KA receptors on I_{sAHP} at the CA1 are also inhibited by G-protein and PKC inhibitors (Melyan et al. 2002; Melyan et al. 2004), but unlike the other processes may also involve the adenylyl cyclase-PKA pathway as activators of or acting next to PKC (Grabauskas et al. 2007).
Although no binding domains have been recognized in KA subunit sequences, functional coupling between $G_{i/o}$ G-proteins and KA receptors have been reported in rat hippocampal membranes and in goldfish (Ziegra et al. 1992; Cunha et al. 1999). It is suggested that the coupling will be mediated by an adaptor protein, since it is thought to be unlikely that the G-proteins dock directly to the KA receptors (Rodriguez-Moreno et al. 1998).

It is believed by some researchers that the GluK1 subunit is responsible for the metabotropic actions in G-protein dependent modulation of Ca^{2+} flux and is functionally coupled to G-proteins (Rozas et al. 2003). The role of the metabotropic action in the presynaptic terminal is to reduce Ca^{2+} channel activity, thereby reducing Ca^{2+} influx and glutamate release. This mechanism could be (in part) responsible for some of the bidirectional effects of KA. At low glutamate concentrations the Ca^{2+} influx runs through high affinity KA receptors and maybe through voltage-gated Ca^{2+} channels. If the concentration glutamate in the synapse increases low affinity KA receptor subunits, like the GluK1 subunit, start getting activated and induce the metabotropic pathway, reducing the Ca^{2+} influx via voltage-gated Ca^{2+} channels and further glutamate release. However, it is still questionable if the GluK1 subunit is present and necessary in all presynaptic terminals.
Moreover, GluK1 agonist ATPA did not produce inhibition of the I_{sAHP}, suggesting lack of involvement in this metabotropic mechanism (Melyan et al. 2002). On the other hand, knock out GluK2 animals, which do not express functional KAR in CA3, show an absence of the I_{sAHP}'s and I_{mAHP}'s in CA3 neurons (Fisahn et al. 2005). In addition, GluK5 is also a candidate for contribution to the I_{sAHP}, lacking an inhibition effect of I_{sAHP} when deleted (Ruiz et al. 2005; Sachidhanandam et al. 2009).

For KA receptors to be able to modulate the synaptic transmission and thereby cognition in the correct way, the receptors must first arrive in the correct amounts on the right locations on the neurons. To assure this happens correctly the trafficking of the KA receptors has to be regulated.

Trafficking

KA receptor trafficking is highly regulated. The exit from the endoplasmic reticulum (ER) determines the number of KA receptors in the plasma membrane and is thereby important for modification of the synaptic strength. Exit from the ER is the most strictly controlled step in the membrane protein transport to the plasma membrane (Ellgaard et al. 2003).
Retention and retrieval in the ER depends on motifs present in the C-terminal of the protein. Examples of motifs are KDEL, KKXX, the RXR motif (X is a neutral or basic amino acid) or arginine-based motifs (Zerangue et al. 1999; Ma et al. 2002). Other processes influencing the preservation of the proteins at the plasma membrane are stabilization of the receptors, retrograde trafficking, localization, desensitization and internalization. There are multiple proteins able to bind to the

KA receptors, all able to influence one of these processes through their interaction. Changes in trafficking of KA receptors probably play an important role in synaptic plasticity.

ER retention

GluK4 and -5 can not form functional homomeric channels, because they are retained at the ER (Gallyas et al. 2003). GluK5 contains a RXR motif, a string of five arginine residues and a di-leucine sequence in the cytosolic tail which causes it to be maintained in the ER (Hayes et al. 2003; Ren et al. 2003a). Coatomer protein complex I (COPI) is responsible for part of the retrograde trafficking of misfolded or unassembled proteins from he Golgi to the ER (Lee et al. 2004). COPI vesicle coat association with the poly-arginine motif in GluK5 prevents surface expression of homomeric assemblies (Vivithanaporn et al. 2006). Disruption of the motifs in GluK5 leads to ER departure and expression in the plasma membrane, but the homomeric receptors remain nonfunctional (Ren et al. 2003a). GluK4 also contains an arginine-rich motif, making it likely it is retained in a similar fashion a GluK5 (Ren et al. 2003a).

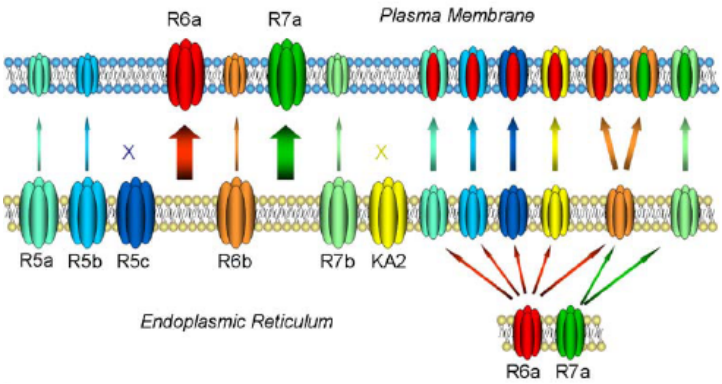

Fig. 6: Membrane trafficking of KA receptor subunits GluK1-3 and -5. Exit from the ER and targeting of the receptors to the plasma membrane depends on the composition in terms of subunits and splice variants (Pinheiro et al. 2006).

The trafficking and surface expression does also differ between the different splice variants. The splice variant GluK1-2c does not occur as homomeric channel on the surface (see Fig. 6), having a RXR motif in addition to some positive charged residues. GluK1-2b also contains a string of positively charged amino acids which are thought to represent an ER retention signal (Ren et al. 2003b). However, GluK3b contains a RXR motif like GluK1-2c and GluK5, and although its surface expression is lower than the GluK3a variant (see also Fig. 6), this does not act as a retention motif (Jaskolski et al. 2005). The other splice variants GluK2a and GluK3a do not occur in the ER and are therefore expressed highly in the plasma membrane (Jaskolski et al. 2004; Jaskolski et al. 2005). This is the result of a cysteine residue followed by a cluster of positively charged amino acids, creating a forward trafficking signal (Yan et al. 2004; Jaskolski et al. 2005). Besides differences in splice variants, editing of the subunits also leads to another distribution between ER and surface expression levels. In case of GluK2, the unedited form exits the ER more efficiently than its edited form (Ball et al. 2010). However, this could not be reproduced in another study (Ma-Hogemeier et al. 2010).

It is thought that at first dimers are formed in the ER and therefore one subunit is able to shield the retention signal of another subunit or is able to structurally alter second subunit (Vivithanaporn et al. 2006; Ma-Hogemeier et al. 2010). The retention in the ER is as a result not only regulated by subunit composition but also by hetero oligomerization. Subunits with high expression in the plasma membrane promote the expression of subunits normally retained in the ER. GluK5 interaction with COPI is for instance reduced when co-expressed with GluK2a and consistently GluK5 plasma membrane expression is shown as heteromeric assembly with GluK2 (Vivithanaporn et al. 2006).

Localization and desensitization
Subsequently to the retention in the ER, next thing controlled by trafficking is the localization of the subunits into the membrane. The localization also depends on the interactions with other proteins. Distribution of KA receptors differs in proximal and distal somatodendrite sites and the axonal compartment.
GluK1 is primarily located in the somatodendritic compartment. Homomeric GluK1 receptors, or heteromeric co-assemblies with GluK3 or -4, are only localized in proximal dendrites, while co-assembly with both GluK2 and -5 leads to localization in the more distal dendrites (Kayadjanian et al. 2007). The localization to distal dendrites is dependent on motor protein KIF17, which probably forms a complex with GluK2 and -5. Knocking out only GluK2 or -5 does not lead to localization of GluK1 in distal dendrites, suggesting that both are needed for GluK1 the targeting. Hence subunit composition is important for the localization of the receptors. It is shown that effective localization of presynaptic GluK2 and -3 receptors near release sites is disrupted in Gluk4 and -5 knock out mice (Fernandes et al. 2009).

Part of the KA receptors is located in postsynaptic densities (PSD) (Hirbec et al. 2003). These are protein networks just underneath the plasma membrane consisting of cytoskeletal proteins, adaptor molecules, cell-adhesion molecules, signalling enzymes and neurotransmitter receptors (Wyneken et al. 2004). The amount of receptors in the PSD determines the postsynaptic response after presynaptic glutamate release and the regulation is thought to underlie the mechanism for synaptic strength and plasticity. Proteins in the PSD contain postsynaptic density-95/Discs large/zona occludens-1 (PDZ) domains which are protein-interaction domains that important dynamic trafficking and membrane organisation (Kim et al. 2004). The C-terminal sequences of both GluK2 and splice variants of GluK1 contain PDZ-binding motifs and can interact with scaffolding proteins (Garcia et al., 1998; Hirbec et al., 2003). Through this motif the subunits can bind the PDZ domain-containing proteins, like scaffold proteins of the membrane-associated guanylate kinase (MAGUK) family, postsynaptic density protein 95 (PSD-95) (also known as synapse-associated protein 90 or SAP90), SAP97 and SAP102. These proteins are highly concentrated in the PSD and associate with NMDA and KA receptors in type 1 glutamatergic synapses (Muller et al. 1996; Garcia et al. 1998).
GluK2/3 and GluK5 subunits are present in the postsynaptic membrane, tightly anchored to PSD (Ball et al. 2010). GluK2(a) and -5 are able to interact with PSD-95, which can cause clustering of KA receptors and reduces the extent of desensitization (Garcia et al. 1998). PSD-95 has a modest affect on the recovery rate from desensitization of GluK2 receptors (Bowie et al. 2003). Gluk2 and –5 are also able to associate with SAP102, while only GluK2 is able to associate with the presynaptic located SAP97 (Garcia et al. 1998; Mehta et al. 2001).

Another PDZ protein interacting with glutamate receptors is glutamate-receptor-interacting protein (GRIP). GRIP is able to directly associate to kinesin motor proteins, thereby recognized as trafficking protein for at least AMPA subunit GluA2 (Setou et al. 2002). GRIP is thought to act as an adaptor protein to crosslink AMPA receptors or associate AMPA receptors with other proteins (Xia et al. 1999). GRIP stabilizes KA receptors at the cell surface, whereas it causes internalisation of the AMPA receptors (see also Fig. 7). GRIP has shown to interact at least with GluK1-2b, -2c and GluK2, while no interaction has been found with GluK1-2a and GluK3a (Hirbec et al. 2003). Protein interacting with protein kinase C (PICK1) is also able to associate with GluK1-2b and GluK2, but not with GluK1-2a or GluK3a (Hirbec et al. 2003). Interaction of PICK1 with GluK2c is not confirmed by all experiments, but this might be because of a low concentration of the complex or misfolding in certain experimental settings. PICK1 is able to increase the peak current and relative desensitisation of currents

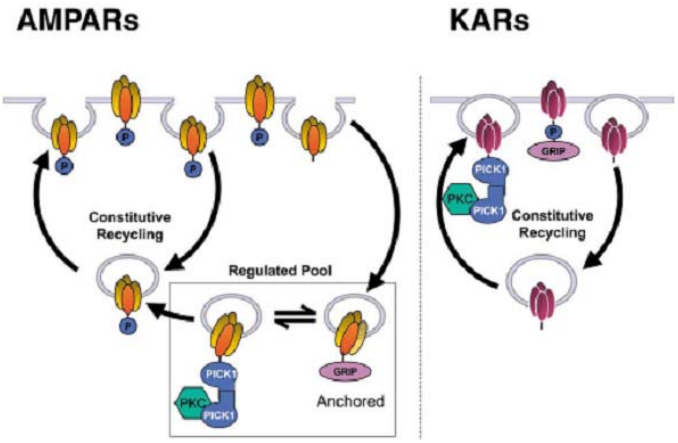

Fig. 7: Model showing the possible mechanisms of differential regulation of functional AMPA and KA receptors by the PDZ proteins PICK1 and GRIP, and by PKC. While AMPA receptors are thought to be internalized after binding to GRIP, GRIP is believed to stabilize KA receptors at the plasma membrane. Picture adapted from (Hirbec et al. 2003)

induced by GluK2 subunits (Laezza et al. 2008). PICK1 may indirectly trigger receptor movement (Perez et al. 2001) and induces AMPA receptor clustering (Xia et al. 1999) and might have the same function for KA receptors. The presence of the AMPA receptor GluA2 leads to prevention of binding of PICK1 to GluK1-2b (Hirbec et al. 2003). Therefore, co-expression of AMPA with KA receptors in the same synapse may lead to different desensitization kinetics. Disrupting either GRIP or PICK1 leads to a rapid loss of functional synaptic KA receptors (Hirbec et al. 2003). The interaction of PICK1 with KA receptor subunits may involve phosphorylation by PKC. PKCα is known to interact with PICK1 (Staudinger et al. 1995; Staudinger et al. 1997) and PICK1 regulates PKC translocation to dendritic spines (Perez et al. 2001). GluK1–2b and GluK2 subunits can be phosphorylated by PKC (Hirbec et al. 2003). The inhibition of PKC causes a rapid reduction in KA-induced EPSC amplitude, mimicking the effect of PICK1 disruption (Hirbec et al. 2003). Interestingly, phosphorylation of AMPA decreases GRIP binding and increases internalization and disruption of GRIP leads to a rapid increase in AMPA-mediated EPSCs (Chung et al. 2000; Daw et al. 2000). This suggests an important role for PDZ-containing interacting proteins in the relative amount of AMPA/KA receptors at synapses.

Protein kinase A (PKA) has also shown to be able to enhance KA-mediated currents by phosphorylation (Wang et al. 1991). A-kinase-anchoring proteins (AKAPs) are known to bind PKA and are required for the modulation of AMPA/KA channels by PKA (Rosenmund et al. 1994). The increase in KA-mediated currents requires PKA to be phosphorylated via activation of adenylate cyclase and cAMP (Greengard et al. 1991). However, since KA and AMPA are both able to bind to KA and AMPA receptors, it is not clear if the PKA-dependence holds true for both KA and AMPA receptors or only for one of them. In the GluK2 sequence a cAMP-dependent protein kinase (PKA) phosphorylation site is reported which may be affected this way (Raymond et al. 1993; Wang et al. 1993). GluK2 can be dephosphorylated by the phosphatase calcineurin which decreases the probability of channel opening (Traynelis et al. 1997). Calcineurin bound to GluK2b can be activated by Ca^{2+} influx through NMDA receptors and thereby decrease KA receptor amplitude in hippocampal neurons and influencing a form of short-term plasticity (Ghetti et al. 2000; Coussen et al. 2005; Rebola et al. 2007).

Cadherin/catenin adhesion proteins are also highly enriched in the PSD. GluK2 is able to interact with β-catenin, cadherins and p120 catenin (Coussen et al. 2002). A role for cadherin/catenin protein is implicated in the targeting and stabilization of GluK2-containing receptors at the synapse. GluK2 also interacts with calmodulin-associated serine/threonine kinase (CASK) (Coussen et al. 2002). CASK is a scaffold protein of the MAGUK family and is present on both sides of the synaptic cleft (Kim et al. 2004). It links PSD proteins, receptors and transporters to cell-adhesion molecules (Coussen et al. 2002). Although the

interaction of β-catenin with GluK2 is indirect, it is not probable that CASK (or PSD-95) is the linking protein in this complex. PSD-95 seems to compete with β-catenin for GluK2 binding (Coussen et al. 2002). Another scaffolding protein suggested to mediate the GluK2-β-catenin binding is syntenin. Syntenin is colocalized with both KA receptors and β-catenin (Zimmermann et al. 2001) and is able to interact with GluK1-2b, -2c and GluK2, but not with GluK2a and GluK3a (Hirbec et al. 2003). High-affinity subunits GluK4 and -5 do not interact with scaffold protein syntenin due to lack of the ODZ-binding motif. Syntenin is tightly developmental regulated and is most abundant during periods of intense neurite outgrowth, synapse formation and synapse stabilization (Hirbec et al. 2005). Overexpression of syntenin increases the amount of dendritic protrusions. It is suggested that the interaction of KA receptors with syntenin plays a role in the formation and maturation of synapses.

KRIP6 is able to bind to GluK2a and thereby reduce the peak current amplitude, but increase the KA-induced steady state current, without altering the plasma membrane localization (Laezza et al. 2007). KRIP6 and PICK1 are strongly co-localized and may compete with each other for GluK2 binding (Laezza et al. 2008), regulating the opposite effects on peak current and desensitization.

As already mentioned previously, KA receptors can bind to intracellular polyamines, like spermine, in a voltage-dependent manner. This interaction leads to a block of the receptor, being the strongest for GluK3 (Perrais et al. 2010). Interestingly, the GluK3 block by spermine is only relieved at hyperpolarized potentials, half of them blocked at -80mV.

Internalization

Internalisation of receptors is balanced in neurons with surface expression through signalling pathways still to be defined. It is reported that KA leads to targeting the receptors to lysosomes for degradation, while NMDA receptor activation can trigger endocytosis of KA receptors to endosomes for recycling (Martin et al. 2004). This latter process is thought to be mediated by Ca^{2+}, PKA and PKC. Furthermore, activation of the GluK5-2b receptor leads to the phosphorylation of two serines in the C-terminal by PKC (Rivera et al. 2007). The activation of PKC by KA receptors is thought to be triggered via the non-canonical KA receptor-signalling pathway (a G-protein) and leads to PKC-triggered endocytosis. So besides the enhancement effect of phosphorylation on KA-induced currents, PKC has also shown to be involved in the internalization of KA receptors.

These opposite roles for PKC suggests that normal/small activity of KA receptors is enhanced by phosphorylation of either PKA or PKC, but at high concentrations of KA PKC phosphorylation leads to increased internalisation as feedback to neuronal overactivation (Rivera et al. 2007). This idea corresponds with the fact that KA receptors show a bidirectional activation (see Biophysical properties) and is confirmed by the observation that increasing the network activity with a $GABA_A$ receptor antagonist also increases the endocytosis of GluK2 (Martin et al. 2004). Furthermore, PKC does not seem to initiate GluK2 internalisation, but only allow this. This would suggest other proteins to be involved in internalisation, maybe only activated by higher levels of activation.

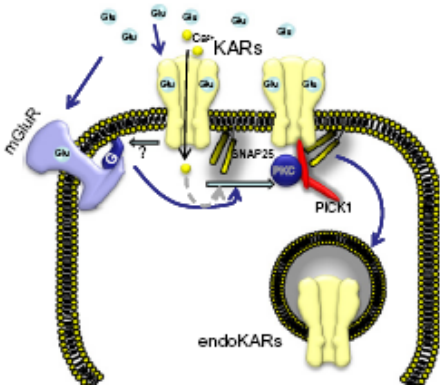

Fig. 8: Internalization of KA receptors triggered by SNAP25 and PICK1 (Selak et al. 2009).

Other proteins reported to be involved in KA receptor internalization are SNAP25 and actinfilin. Scaffolding protein SNAP25 is increased after a KA injection

(Boschert et al. 1996) and has a role in internalisation of KA receptors containing the GluK5 subunit from the synapse (Selak et al. 2009). This interaction may be supported by PKC-regulated interactions with PICK1 and might involve metabotropic glutamate receptors (see also Fig. 8). For GluK2 the degradation is influenced by the interaction with actinfilin which via binding to Cullin 3 (cul3) targets GluK2 to the E3 ubiquitin-ligase complex (Salinas et al. 2006).

Since the different subunits, subunit assemblies, splice variants and editing states show dissimilarities in binding ligand and permeability, the differences in trafficking may help to regulate getting the right subunit assemblies to the right spot in the neuron and increase the amount of functions of KA receptors.

One of these functions is the modulation of synaptic strength and plasticity. The most studied form of synaptic plasticity modulated by KA receptors is long-term potentiation, abbreviated to LTP.

Long-term potentiation

LTP is an experimentally induced form of synaptic plasticity which his thought to underlie learning and memory, and thereby an important part of cognition. Glutamate is well known for its role in mediating excitatory synaptic transmission and synaptic plasticity. Although most research underscores to the role of the two other ionotropic glutamate families AMPA and NMDA receptors, KA receptors are also involved in LTP. There are two types of LTP. The major type of LTP is input-specific, associative, coincident NMDA-dependent LTP, also referred to as Hebbian-LTP (Urban et al. 1996). This LTP requires simultaneous activity of both the pre- and postsynaptic neuron. The second type of LTP occurs in mossy fibers in the hippocampus and is non-associative and NMDA-independent (Harris et al. 1986; Chattarji et al. 1989; Zalutsky et al. 1990; Katsuki et al. 1991). In the latter LTP KA receptor are thought to have an important role. The activity in the presynaptic neuron is enough to produce LTP if the firing rate is rapid (Nestler et al. 2001).

Associative LTP
Associative LTP is the most common and known form of LTP. After glutamate release from the presynaptic neuron AMPA receptors are opened and cations move through the pore. NMDA receptors are blocked by extracellular Mg^{2+} ions which reside in the NMDA receptor pore at resting potentials (Bliss et al. 1993). Due to the cation current through the AMPA receptors the membrane depolarizes and the Mg^{2+} ion is expelled from the channel. Glutamate binding to the NMDA channel will now lead to opening of the channel and an influx of Ca^{2+}. So coincident activity of both the presynaptic and postsynaptic neuron are necessary to activate the NMDA receptor and induce NMDA-dependent LTP (Stevens et al. 1998). How this activation of NMDA receptors exactly leads to long-term enhanced synaptic potentiation is however still not known. The intracellular increase in Ca^{2+} is thought to be important in the mechanisms to decrease the threshold and formation of the LTP (Bliss et al. 1993; Platenik et al. 2000). The Ca^{2+} influx may lead to activation of Ca^{2+}/calmodulin-dependent kinases (CaMKs), PKC and tyrosine kinases Src and Fyn (Vaccarino et al. 1987; Stevens et al. 1994; Chen et al. 1998; Huang 1998; Lu et al. 1998; Salter 1998). CaMKII has shown to be necessary for the induction of LTP and synaptic plasticity (Soderling 2000; Lisman et al. 2002). Kinase activity is thought to be important especially in the early phase of LTP (E-LTP) (Huang 1998). Tyrosine kinase Src leads to phosphorylation and thereby to an increase in NMDA receptor functioning, thus enhancing the chance of subsequent activation of the NMDA receptors (Lu et al. 1998; Salter 1998). NMDA receptors furthermore increase the Ras/MAP kinase

pathway, probably also via Ca^{2+} influx and CaMK activation (see Fig. 9) (Chen et al. 1998; Platenik et al. 2000).
The induction of gene transcription and subsequent new protein synthesis is thought to be involved in the late phase of LTP (L-LTP) (Frey et al. 1988; Nguyen et al. 1994; Huang 1998). Immediate early genes, like c-Jun and c-Fos, are also induced after glutamate administration and blocked by NMDA antagonists (Platenik et al. 2000). These immediate early genes form dimers (AP1) and increase DNA transcription via binding to CRE or TRE consensus DNA sequences. Another pathway induced by NMDA receptors is the c-Jun terminal kinase (JNK) pathway. The activation of the JNK pathway (or one of its members named stress-activated protein kinase (SAPK)) does however not need extracellular Ca^{2+} influx, but depends on Na^{+} influx (Schwarzschild et al. 1999). Activation of SAPK has the opposite effect of ERK (one of the members of the Ras/MAP kinase pathway) on physiological processes, e.g. cell survival. This might explain the different effects of NMDA receptors when extracellular calcium and sodium levels are changed and might be a mechanism to differentially regulate cellular functions upon glutamate release (Schwarzschild et al. 1999). It is possible that the JNK pathway is just like cell death-inducing MAPK p38 involved in LTD (Li et al. 2006).

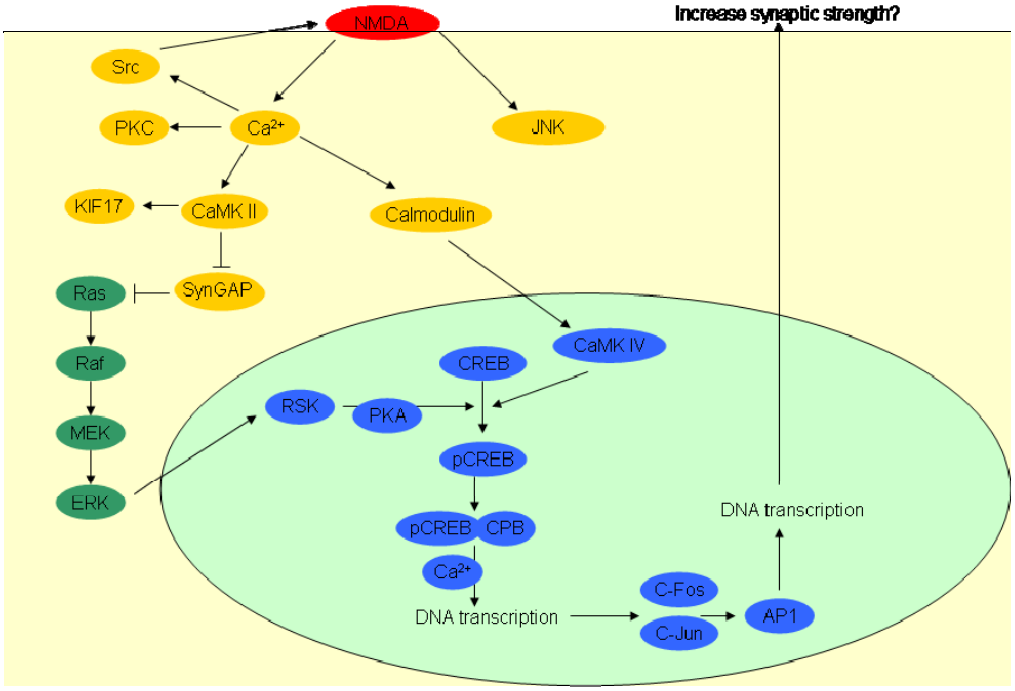

Fig. 9: Major pathways proposed how NMDA-receptor activation can lead to LTP induction. Ca^{2+} can move through NMDA receptors when these channels open and this leads to activation of PKC, CaMKII and calmodulin. Via the activation of phosphorylation cascades CREB is activated and DNA transcription increases. The new protein synthesis is thought to be an important aspect of LTP induction.

Non-associative LTP
Non-associative LTP does only occur at a few synapses in the brain. In the mossy fiber pathway in the hippocampus, which runs from the dentate gyrus up to the CA3 region, only presynaptic activity seems to be sufficient for inducing LTP (Zalutsky et al. 1990; Weisskopf et al. 1995; Alle et al. 2001). However, it is reported that besides the non-Hebbian type also Hebbian LTP can occur in the mossy fibers (Jaffe et al. 1990; Urban et al. 1996). The type of LTP induced in mossy fibers seems to depend on the specific pattern of stimulation used in the study (Henze et al. 2000). The involvement of presynaptic KA receptors in synaptic facilitation or depression is shown in mossy fibers in the hippocampus as well as in the cerebellum, amygdala and thalamocortical transmission.

In mossy fibers presynaptic KA receptors cause a positive feedback loop, by stimulating glutamate release after being activated after the first voltage-dependent glutamate release. If the glutamate concentration in the synaptic cleft becomes too high, the positive feedback loop will however be shifted to a negative feedback loop, inhibiting further glutamate release. Although it is believed by one group that presynaptic receptors play an important role, another group thinks the presynaptic receptors are involved in LTP by adjusting the induction threshold, but are not essential for the induction like stated by the others (Schmitz et al. 2003). This last conclusion is drawn based on experiments performed with high cation (Ca^{2+} and Mg^{2+}) levels, which may be the cause for the difference in conclusion.
Although depletion of Ca^{2+} does not affect short-term plasticity (Carter et al. 2002), in both associative and non-associative LTP Ca^{2+} seems to play an essential role (Lauri et al. 2003). This could mean that the same pathways are induced as by NMDA receptor-dependent LTP. Upon activation and opening of Ca^{2+}-permeable KA receptors, the Ca^{2+} influx causes a release of Ca^{2+} from intracellular stores, which is important for inducing mossy fiber LTP (Lauri et al. 2003). Ca^{2+} is also able to enter the cell via different receptors, like the L-type Ca^{2+} channels, and these receptors are able to compensate for the Ca^{2+} influx via KA receptors (Bortolotto et al. 2005). Blockade of voltage-gated, L-type Ca^{2+} channels abolishes/reduces KA receptor induced LTP. High extracellular Ca^{2+} concentrations (4mM) are able to abolish the need for KA receptors in LTP induction, whereas blockade of the channels leads to dependence on KA receptors (Lauri et al. 2003). Therefore, the amount of synaptic strength and amount of influence of (specific) antagonists on LTP function also depends on the amount and relative levels of cations. With high levels of Ca^{2+} in the medium, blockade of for example GluK1 receptors will not be able to block LTP entirely. The role of the GluK1 subunit may therefore be underestimated in a few studies. Some of the literature showing that GluK1 deficiency did not affect mossy fiber EPSPs and LTP was performed in medium with high levels of cations (Contractor et al. 2000; Contractor et al. 2001).
In contrast to the presynaptic data, the intracellular Ca^{2+} levels do not seem to effect the efficacy of synaptic transmission by postsynaptic KA receptors (Wyneken et al. 2004) and mossy fiber LTP is reported to be independent of postsynaptic calcium and membrane potential (Mellor et al. 2001). The opposite is also reported, claiming a required increase in postsynaptic calcium levels for the induction of mossy fiber LTP (Williams et al. 1989; Yeckel et al. 1999).

It is reported that PKC, which can be activated upon an increase in intracellular Ca^{2+}, has a role in mossy fiber LTP induction, although involvement of KA receptors was not investigated in this study (Son et al. 1996; Alle et al. 2001). Interestingly, in this study PKA was not involved in the LTP induction, while both PKC and PKA were involved in the short-lasting posttetanic potentiation (PTP), showing distinct roles of the two protein kinases in synaptic plasticity. In support of this finding one of the substrates of PKC, GAP-43, shows increased phosphorylation after the induction of mossy fiber LTP and is implicated in the release process and synaptic plasticity (Son et al. 1996; Holtmaat et al. 1997; Oestreicher et al. 1997; Son et al. 1997).

The slow deactivation kinetics of KA receptors allows substantial tonic depolarization during modest activity in the presynaptic neuron. Through this mechanism KA receptors may be able to enhance the relative importance of single inputs by bringing the membrane potential closer to the spike threshold (Lerma 2003). This increase in duration will increase the chance of exceeding the threshold, but will by far not be long enough for the changes needed to induce LTP. The second messenger pathways KA induces can be the sources of LTP induction. The second messenger pathways are longer active compared to the KA

receptors themselves after glutamate release and might therefore mediated the cellular changes needed for prolonged increased synaptic stimulation/transmission. MAP kinases are part of some second messenger pathways, like published for the associative LTP induction. MAP kinases are thought to be involved in both NMDA receptor-dependent and –independent LTP (English et al. 1996; Coogan et al. 1999). All three ionotropic glutamate receptors are believed to activate ERK1/2 in a Ca^{2+} influx-dependent manner and increase CREB phosphorylation (Mao et al. 2004). ERK is thought to be important in the E-LTP (Winder et al. 1999), while the activation of transcription factor CREB will enhance gene expression, needed for the L-LTP effect. The activation of MAP kinases by KA is furthermore thought to mediate its effect on the I_{sAHP} in the CA1 region (Grabauskas et al. 2007) and on apoptosis in the cerebellum (Cheung et al. 1998; Giardina et al. 2002). This last effect is mediated by p38 (Giardina et al. 2002) and c-Jun (Cheung et al. 1998), the last possibly activated via the JNK pathway. Like NMDA receptors, KA receptors are also linked to the JNK pathway, but it is unclear if this is connection is involved in LTP modulation. Association of GluK2 with PSD-95 leads to binding of mixed lineage kinase 3 (MLK3) to the SH3 domain of PSD-95. This leads to autophosphorylation of MLK3 and subsequently to activation of c-Jun NH2-terminal kinase 3 (JNK3) (Tian et al. 2005). The interaction between GluK2a and PSD95 might be able to trigger the KA-induced excitotoxicity via the MLK2/3, JNK pathway (Savinainen et al. 2001).
Since the same secondary pathways seem to be activated after NMDA and KA receptor activation, it is likely that LTP induction by KA receptors is also mediated by the pathways shown in figure 9.

At the mossy fibers the GluK1 antagonist LY382884 blocks presynaptic but not postsynaptic KA receptors at levels which block LTP (Lauri et al. 2001a). This would suggest that presynaptic GluK1 containing KA receptors are responsible for the induction of mossy fiber LTP. The presynaptic receptor is thought to facilitate the EPSC inductions in mossy fiber neurons and by facilitating AMPA receptor-mediated synaptic transmission (Lauri et al. 2001a). However, like discussed in a previous section, GluK1 expression in postsynaptic CA3 neurons is very weak (Bahn et al. 1994), which makes the significance of this subunit less probable. Since LY382884 only inhibits presynaptic receptors, it is thought that GluK1 is not a component in postsynaptic CA3 cells (Breustedt et al. 2004). Furthermore, GluK1-deficient mice have normal LTP at mossy fiber synapses and antagonist LY382884 does not affect mossy fiber LTP (Contractor et al. 2001; Breustedt et al. 2004). However, compensatory mechanisms in knock out animals might be responsible for these effects, and the GluK1 subunit may therefore still have a function in wild-type mossy fibers.
Interestingly, LTP at the associational/commissural fibers of the hippocampus and at CA1 synapses are resistant to the GluK1 antagonist LY382884 (Bortolotto et al. 1999), confirming the idea that these synapses are mediating NMDA-dependent LTP.

Gene knockouts of GluK2 support a role for this subtype in LTP and synaptic facilitation (Contractor et al. 2001). GluK2 influences the magnitude of the LTP. Short- and long-term KA induced synaptic facilitation in hippocampal mossy fibers is abolished by knocking out GluK2, while knocking out or antagonizing GluK1 did not affect these processes (Mulle et al. 1998; Contractor et al. 2001; Breustedt et al. 2004). This is not an unexpected finding, since it was shown before that GluK1 deficiency does not change mossy fiber EPSCs compared to wild-type, while knocking out GluK2 abolishes the reduction of the EPSCs (Contractor et al. 2000). In addition, GluK2 deficiency, but not GluK1 deletion, impacts the LTP in substantia gelatinosa and the expression of Ca^{2+} transients, but does not influence LTD (Youn et al. 2005).

The permeability of Ca^{2+} for GluK2 receptors depends on the amount of editing. Therefore, the amount of Ca^{2+} influx and thereby the size of synaptic strength will depend on the relative proportions of edited GluK2. The editing of GluK2 subunits might therefore play an important role in regulating LTP. Unedited GluK2 subunits mediate the LTP, while mice which are able to perform editing did not. However, the mutant mice without editing were more vulnerable to KA-acid-induced seizures (Vissel et al. 2001). So the editing of the receptors requires right relative amounts for regulation of LTP and vulnerability to seizures.

The presynaptic located GluK3 subunit is also involved in LTP induction. Deficiency of this subunit does not block LTP completely, but reduces the mossy fiber LTP (Pinheiro et al. 2007). This reduction can be rescued by increasing extracellular K^+ levels and changing the induction protocol, so experimental conditions determine if GluK3 will play a role in the induced LTP. The GluK4 subunit has not been tested for its role in LTP. Although GluK5 is thought to be at least part of the postsynaptic receptors and is also found presynaptically, GluK5 doesn't seem to play a role in mossy fiber LTP, since deficiency of this gene does not change LTP induction (Contractor et al. 2003).

Besides the hippocampus, KA- mediated LTP can also be evoked in other brain areas like the amygdala. EPSPs evoked by external capsule stimulation and recorded in the BLA are partially mediated by KA receptors (Li et al. 1998). Low frequency stimulation in the amygdala has shown to exert a progressive enhancement of transmission, which is mimicked by GluK1 agonist ATPA and blocked by GluK1 antagonists, but not by AMPA or NMDA antagonists (Li et al. 2001). Although this suggests homomeric GluK1 receptor involvement in amygdala LTP, ATPA has also shown to bind to GluK1/-2 and GluK2/-5 heteromeric receptors (Paternain et al. 2000) and some antagonist are known to bind to heteromeric receptors. Furthermore, in the amygdala LTP is blocked by GluK2 knockout, but not affected by GluK1 knockout. The potentiation seen in the amygdala was not only present in the stimulated fibers, but was generalized to other inputs, like the basal amygdala (Li et al. 2001).

Cognition

Although cognition is more than only memory, cognitive enhancers are mostly searched in learning-and memory enhancing substances. Other processes falling under the term cognition are also association, attention, language, concept formation and problem solving (Sharma et al. 2010). Cognitive enhancers are now sought in molecules influencing the NMDA receptors or the enzyme acetylcholinesterase (AchE). NMDA receptor agonists are able to enhance the associative LTP and thereby increase cognitive functioning. The AchE inhibitors increase acetylcholine (Ach) in the synaptic cleft, consequently enhance synaptic transmission in synapses which release Ach and improve learning (Muthuraju et al. 2010). In addition, noradrenaline (NA) is thought to influence memory formation. B-adrenergic receptor activation is involved in LTP and antagonist can prevent enhancement of memories by emotion.
Since the research for KA receptor function is only started recently, there is not much evidence yet for a straightforward role of KA receptors in cognition. There are however some indications that implicate a role for KA receptors in these processes. There are different ways in which KA receptors could lead to cognition enhancement. Some of these mechanisms could underlie the same mechanisms as the substances mentioned above, which are already used for this purpose.

The effect of these drugs may vary for different types of memory. There are different structures composed of various neurotransmitter systems and involved

in different memory types. The hippocampus is involved in the consolidation of memory and in spatial memory (McNaughton et al. 1986; Zola-Morgan et al. 1990; Poucet et al. 2010) and is probably the most widely studied because of its architecture. In the hippocampus the mossy fibers are believed to play an important role in memory storage and retrieval (Bischofberger et al. 2006). The amygdala is involved in emotional memories (Cahill et al. 1995; LeDoux 2000).

Acetylcholine modulation
AchE inhibitors, like galanthamine or metrifonate, are used in Alzheimer's disease, which is characterized by progressive loss hippocampal neurons and cognitive/memory functions (Nestler et al. 2001; Bertram et al. 2010). Through enhancing the Ach level in the synaptic cleft, it is believed that the symptoms of the patients decrease. The cholinergic nucleus, nucleus basalis, projects heavily to the neocortex and hippocampus. Ach induces a synchronized firing, known as the θ rhythm, which facilitates memory formation, probably through lowering the neural activity threshold. Interestingly, muscarine Ach receptors can modulate KA subunit activity (Benveniste et al. 2010). This has been shown for heteromeric GluK2 receptors, like GluK2/GluK4 and GluK2/GluK5, but not for homomeric GluK2 receptors. Therefore, targeting the muscarinic Ach receptors may be a way to indirectly modulate KA receptors, which could be the responsible receptors for the memory enhancement.

Oscillatory network activity
Increased excitation can lead to rhythmic activity in neuronal networks which produces oscillations in different frequency bands. Oscillations in the γ frequency (20-80Hz) band are believed to play an important role in learning, memory and cognition (Singer 1993; Buzsaki et al. 1995; Fisahn et al. 2004). This is further supported by the finding that Alzheimer patients show modified temporal and spatial organization of the 40Hz activity (Ribary et al. 1991). KA receptors are reported to induce extracellular γ oscillations, which arise from synchronized intracellular currents (Fisahn et al. 2004). These effects are enhanced in mice lacking the GluK1 subunit, while they are ablated in GluK2 knock out mice. The different roles of the two subunits may be due to their location (Fisahn 2005). GluK1 subunits are highly expressed in GABAergic interneurons (Paternain et al. 2000), modulating GABA release and IPSCs, while GABA receptors are also involved in γ oscillations. Γ oscillations are reported to be dependent on $GABA_A$ receptors (Oke et al. 2010), while $GABA_B$ receptors have shown to both mediate slow oscillations as modulate the power and spatial profile of γ oscillations (Kohl et al. 2010). GluK2 subunits are also believed to modulate GABAergic transmission, but might play a more prominent role on glutamatergic synaptic transmission.
Next to KA also Ach agonist carbachol is able to induce γ oscillations (Buhl et al. 1998). This effect is probably mediated by the M1 receptor, since activation by muscarine leads to an increase in γ oscillations and this increase is absent in $M1^{-/-}$ mice (Fisahn et al. 2002). On the other hand, deletion of one of the other muscarine subunits, M2-M5, did not affect the γ oscillations.

In addition to γ oscillations, GluK1 subunit inhibition leads to a reduction in the hippocampal θ (4-12Hz) oscillation frequencies (Huxter et al. 2007). This study reported significant changes in the activity in interneurons. Together with the finding that θ oscillations are prominently controlled by interneuron activity (Lee et al. 1994), this confirms the idea that the effects of GluK1 on oscillations are (partially) the effect of modulation of interneuron activity. The other part of the θ oscillation is under control of cholinergic neurons, which regulate the magnitude of the hippocampal the θ oscillations (Lee et al. 1994; Apartis et al. 1998).

In epilepsy the rhythmic bursts and oscillations frequency are modulated. KA receptors are highly implicated in epilepsy (Sander et al. 1997; Izzi et al. 2002; Dudek et al. 2004; Lerma 2004; Rodriguez-Moreno 2006; Stafstrom 2006; Vincent et al. 2009) and KA itself can induce epileptogenic bursts (Nadler et al. 1981; Ben-Ari 1985). In addition to γ oscillations, GluK2$^{-/-}$ animals are also unable to induce epileptiform bursts (Fisahn et al. 2004). In some types of epilepsy learning and memory deficits and cognitive decline are present (Viskontas et al. 2000).

Slow AHP current
The slow AHP current, which is inhibited by KA receptors, is associated with learning. A reduction in this current is shown after acquisition or conditioning after different tasks, but is not seen after pseudoconditioning (Disterhoft et al. 1986; Coulter et al. 1989; Moyer et al. 1996; Giese et al. 1998; Saar et al. 2001). This reduction leads to learning-specific increased postsynaptic excitability, positively affecting memory performances (Disterhoft et al. 1986; Disterhoft et al. 1988; Moyer et al. 1996). The reduction is necessary during the acquisition and consolidation phase, but not in later phases since the current returns to baseline while behavioral performances remain (Moyer et al. 1996). Interestingly, the slow AHP current increases during aging and this increase is associated with reduced learning capacity (Disterhoft et al. 1996; Kaczorowski et al. 2009; Matthews et al. 2009). Furthermore, the L-type voltage-dependent calcium channels (VDCC), which functioning is necessary for producing the slow AHP current, is important for recognition memory (Seoane et al. 2009).
Besides KA receptors, activating Ach receptors by agonists or increasing Ach concentration with galanthamine or metrifonate also leads to inhibition the I_{sAHP} (Disterhoft et al. 1999; Saar et al. 2001; Ohno et al. 2004; Oh et al. 2006). Blocking muscarine receptors blocks this reduction (Disterhoft et al. 1999) and leads a slower learning process, but does not affect memory when the initial learning took place before the blockade (Saar et al. 2001). In addition to this, β-receptors are also reported to be involved in I_{sAHP} modulation, reducing the current when activated by isoproterenol (Grabauskas et al. 2007). So through modulation of the slow AHP current KA receptors can enhance learning and memory in the same way as AchE inhibitors and β-adrenergic receptor activation.

Stress induced memory
Stress is thought to have an important impact on our ability to learn and memorize (Krugers et al. 2010). The stress hormone corticosterone is able to bind to two different receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Activation of MRs is believed to maintain glutamatergic transmission in the CA1 region of the hippocampus. GR activation is thought to suppress synaptic transmission and plasticity. Furthermore, both receptors alter the frequency of mEPSCs in the hippocampus and amygdala. This is probably the consequence of increased presynaptic glutamate release. GRs are involved in the consolidation of memories and a mutation in the GR leads to impairment of spatial memory performance. Glucocorticoids have shown to regulate AMPA trafficking, increase surface expression and thereby enhance synaptic efficiency (Martin et al. 2009; Conboy et al. 2010). This effect required new protein synthesis. However, the facilitation depends on the synaptic context and can change into loss of AMPA receptors and LTD (Martin et al. 2009). It is suggested that the neural cell adhesion molecules N-cadherin is involved in the synaptic facilitation by corticosterone (Conboy et al. 2010). N-cadherin is shown to interact with the GluA2 subunit for the growth and formation of dendritic spines (Saglietti et al. 2007).
Glucocorticoids also have an effect on KA receptors. Adrenalectomy causes a depletion of corticosterone and increases GluK2, -3 and -4 mRNA levels in the hippocampus (Hunter et al. 2009). Treatment with corticosterone reverses the

enhancement for GluK3 and -4, while aldosterone reverses the effect for GluK2. Chronic restrained stress and a moderate corticosterone dose also elevated the mRNA levels of GluK4. It is not known yet if these effects of corticosterone on KA receptors directly influence learning performances.

Synaptogenesis

A way for KA receptors to induce cognitive enhancement is by increasing synaptogenesis. LTP induction is associated with induction-specific remodelling of the postsynaptic membrane, followed by an increase of spines and contacts between the axon terminal and dendritic spines (Engert et al. 1999; Maletic-Savatic et al. 1999; Toni et al. 1999). By increasing the amount of synapses between two neurons, the probability of inducing an axon potential is enhanced. NMDA-receptor blockade prevents the dendritic morphogenesis in response to the synaptic activity (Maletic-Savatic et al. 1999). AMPA receptors are AchE-dependently upregulated in areas undergoing synaptogenesis (Olivera et al. 2003a; Olivera et al. 2003b). Inhibition of NMDA or AMPA receptors leads to a decrease in neurogenesis and synapsin-I, which is involved in synaptogenesis (Ferreira et al. 1996; Bernabeu et al. 2000). KA receptor activation may also be involved in synaptogenesis induction. GluK1 transcripts are found to have the highest expression in areas where synaptogenesis is in progress (Bettler et al. 1990). Secondly, KA is able to induce the protein F1/GAP-43 in rat hippocampi (McNamara et al. 1995), a protein which is highly expressed in growing axons during synaptogenesis (Benowitz et al. 1988; Benowitz et al. 1989). Furthermore, KA receptors have shown to regulate motility of axonal filopodia (Tashiro et al. 2003). Dynamic filopodia are thought to be important at the initial stages of synaptogenesis (Ziv et al. 1996; Jontes et al. 2000). The movement of axonal filopodia can be inhibited by glutamate, an effect which can be blocked by CNQX, implicating the role of AMPA and/or KA receptors (Chang et al. 2001). Low concentrations of KA increase the motility, stimulating synapse formation, while higher concentrations decrease motility and freeze growth cone movement (Tashiro et al. 2003; Hirbec et al. 2005).

Cell-adhesion molecules (CAMs) are important components of synapses and are also believed to play a role synaptic plasticity (Murase et al. 1999; Benson et al. 2000; Bozdagi et al. 2000; Coussen et al. 2002). CAMs are crucial for the building and maintenance of synapses and can thereby be part of regulating synaptic strength. The GluK2 subunit has shown to interact with CAM molecules like cadherins, p120 catenin and β-catenin (Coussen et al. 2002). For fulfilling their functions, classical cadherins have to interact with catenins (Benson et al. 2000). β-Catenin, which is targeted to KA receptors, is a critical mediator of dendritic morphogenesis (Yu et al. 2003), probably mediating KA receptor effects on synaptogenesis and possibly also on cognition. CAMs have mostly been implicated in fear memory (Merino et al. 2000; Lopez-Fernandez et al. 2007; Bisaz et al. 2010).

Fear memory

KA receptors containing the GluK1 subunit are thought to be involved in synaptic plasticity in the basolateral amygdala (Braga et al. 2003). Low frequency stimulation or ATPA perfusion (a GluK1 agonist) leads to a progressive enhancement of evoked EPSCs amplitude, which persists after termination. This effect is absent after GluK1 antagonist application. This effect of KA receptors on synaptic plasticity in the amygdala may contribute to KA effects on cognition. However, contextual and auditory fear-memory, which is thought to involve the amygdala, is reduced in mice lacking the GluK2 subunit, but is intact in mice lacking the GluK1 subunit (Ko et al. 2005). Additionally, the synaptic potentiation in the lateral amygdala and auditory cortex is reduced in GluK2, but not in GluK1 knock-out mice. This supports the implication that KA receptors are involved in

regulating fear memory. The role of the GluK1 subunit in the amygdala-mediated memory forms is however still questionable.

Spatial and motor memory
Although editing is thought to be important for the physiological properties of KA receptors and thereby also for its function, it has been shown that disrupting GluK1 editing does not lead to differences in motor- and spatial learning, tested with the rotarod test and the Morris water maze (Sailer et al. 1999).
Although GluK2-/- mice have shown to have reduced contextual and auditory fear memory, they show normal Morris water maze performance (Mulle et al. 1998; Ko et al. 2005). However, GluK1-2 and GluK2 subunits are reported to be upregulated after water-maze training (Cavallaro et al. 2002), suggesting KA subunit increase during spatial memory acquisition.

The protein KIF17, that is important for the GluK1/2/5 trafficking to distal dendrites, enhances spatial and working memory (Wong et al. 2002). Furthermore, a mouse model for Down syndrome (DS) showed a significant decrease in KIF17 protein in the brain, which may partly mediate the cognitive defects in DS (Roberson et al. 2008).

Recognition memory
The perirhinal cortex is thought to be involved in recognition memory (Meunier et al. 1993; Suzuki et al. 1993; Ennaceur et al. 1996). Both KA and NMDA receptors are involved in this type of memory, although in a different way. KA receptor inhibition with UBP302 leads to amnesia when injected 20 minutes before testing, but not when injected 24h before testing, while NMDA receptor inhibition only leads to amnesia when injected 24h before testing (Barker et al. 2006). So, there are two mechanisms involved in recognition memory and KA receptors are involved the fast-onset plasticity of recency and novelty responses.

Discussion

The knowledge about the function of KA receptors has been lacking compared to the other ionotropic glutamate receptor subtypes, the NMDA and AMPA receptors. This is mainly due to the overlap of AMPA and KA receptor ligands and the lack of specific antibodies and pharmacological tools. The role of KA receptors is hard to study because of the differences in function and properties between receptor compositions, subcellular localization, and subsequent activated pathways and the contrary results. The contrary results may in part be due to differences in species used in the compared studies. It has been shown that the effect of KA on protein F1/GAP-43 gene expression is different in rat and mouse hippocampus (McNamara et al. 1996). Differences in results due to species differences has also been argued in other studies (Marchal et al. 2004). Besides of species differences, the amount of receptors and relative amount of the subunits also differs per age (Bahn et al. 1994). This might mean that using animals with a different age leads to altered effects, due to dissimilar relative amounts of subunits leading to a different contribution of these subunits to the effects. Especially the GluK1 and GluK2 subunits have shown to have opposite effects. GluK1 is believed to be neuroprotective (Xu et al. 2008), while inhibition of the GluK2-interaction domain leads to neuroprotection (Liu et al. 2006) and they have contrary effect on γ oscillations (Fisahn et al. 2004). Therefore the two subunits may have opposite effects on neuronal excitability and synaptic facilitation (Frerking et al. 2000). The GluK2 subunit enhances neuroexcitability and LTP and agonists for this subtype will be preferred for enhancing cognition. On the other hand, the GluK1 subunit might decrease neuroexcitability and thereby synaptic facilitation and antagonizing this subunit might lead to cognitive enhancement. However, it is not

known what the effect of heteromeric GluK1/2 receptors is on neuroexcitability and cognition and the affinity of new compounds for these receptors should be carefully investigated.
The bidirectional effect of most agonists on KA receptors makes it even harder to draw clear conclusions on their function. Furthermore, the experimental conditions determine to a high degree the outcome. It is however believed that KA receptors play an important role in different brain areas and are implicated in different diseases. A role of KA receptors in cognition is very probable, but the relative significance and the mechanism(s) behind this function are still very unclear. Part of the mechanisms might be overlapping with the mechanisms of systems that already targeted for cognition enhancement. KA receptors and muscarinic Ach receptors show different overlapping effects. NMDA receptors are activated by the same neurotransmitter and colocalization on the same neurons with KA receptors may take place, increasing the chance of collaborative or parallel functioning.

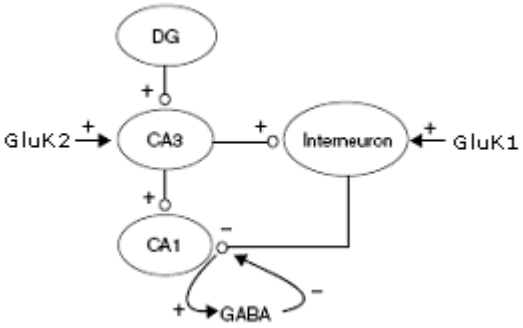

Fig. 10: GluK1 and GluK2 may have opposing roles in hippocampal excitability. GluK1 subunits excite inhibitory interneurons which in turn inhibit CA1 neurons, while GluK2 subunits excite CA1 neurons via CA3 neurons. Picture adjusted from (Frerking et al. 2000)

To be able to make KA receptors a target for cognitive enhancement, a lot more data about the receptors should be collected. Which subunit compositions exist in vivo? What is the exact role of the different subunits and subunit compositions? What type of receptor is important for cognitive enhancement? What is the localization of these receptors? Are there interacting proteins involved in enhancing or decreasing the KA receptor-induced cognition?
If these questions can be answered, it is still uncertain if the right agonist or antagonist can be made. Due to high structural similarity it will be difficult to develop specific ligands, as has been the main reason for lack of knowledge about the KA receptors till now. Moreover, agonists and antagonist used now are not as selective as believed at first. Especially different GluK1 ligands are more and more identified as less selective ligands, binding also to heteromeric GluK1 receptors and GluK2/-5 receptors (Christensen et al. 2004; Jane et al. 2009). This makes it even more difficult to gauge the value of pharmacological determined subunit properties.
Through the differences in effects of KA in diverse brain areas, it may not be possible to enhance all aspects of cognition with one farmacon applied systemically. While trying to enhance for example spatial memory through modulating KA receptors, other aspects of cognition might be decreased. Furthermore, precise concentrations at target sites should be established, due to the bidirectional effects of KA receptors.
Another possibility could be targeting the KA receptors indirectly via interacting proteins, which modulate their function. These proteins play important roles in determining the amount of KA receptors on the plasma membrane and thereby the magnitude of KA receptor involvement in the synaptic transmission and facilitation. PKC is a protein highly involved in KA receptor function, but is also involved in a lot of other processes, making it an aspecific target. Less aspecific proteins may be KIF17 and NETO1/2, which could be investigated for there role in cognition in relation to modulation of KA receptor activation. KIF17 is already related to enhancement of cognition and might be a useful target.

Although KA receptors could be possible targets for cognitive enhancement, we should not forget the other functions they have in the brain. KA is highly implicated in epilepsy (Sander et al. 1997; Izzi et al. 2002; Dudek et al. 2004; Lerma 2004; Rodriguez-Moreno 2006; Stafstrom 2006; Vincent et al. 2009) and

experiments are being conducted to investigate KA receptors as possible therapeutic targets for epilepsy. It is however still not clear if KA receptor agonists will behave as anticonvulsants, through increasing tonic inhibition, or will behave as proconvulsants, through producing an overall disihibition (Lerma 2003). Interfering with KA receptor function for inducing cognition, will lead to differences in neuronal excitability and may induce epilepsy as a side effect.
An example to highlight the significance of this concern is the effect reported when adjusting the editing of the GluK2 subunit. For enhancing LTP and cognition it is favourable to inhibit GluK2 editing (Vissel et al. 2001). However, this leads to a higher susceptibility to KA-acid-induced seizures. Furthermore, deficiency in the total GluK2 subunit leads to a reduction in susceptibility to seizures (Mulle et al. 1998), while it also leads impairment of short- and long term potentiation (Contractor et al. 2001). Enhancing cognition will in this case probably not weigh up to the risk of enhancing seizures.
KA receptors have also shown to be involved in other physiological processes and diseases. KA receptors are involved in different sensory processes, which can be affected when targeting the receptors for cognition enhancement. KA receptors are present in the retina, mediating transmission between cone photoreceptors and off bipolar cells (DeVries et al. 1999; DeVries 2000). In addition, they are involved in taste and pain perception (Ruscheweyh et al. 2002; Chung et al. 2005; Wu et al. 2007; Lee et al. 2009). KA receptors have also been associated with diseases like schizophrenia (Begni et al. 2002; Shibata et al. 2006; Ahmad et al. 2009; Djurovic et al. 2009; Kilic et al. 2010) (Bah et al. 2004), Huntington's disease (Rubinsztein et al. 1997; MacDonald et al. 1999), depression (Schiffer et al. 2007), obsessive compulsive disorder (Delorme et al. 2004), ALS (Gregor et al. 1993b) and autism (Jamain et al. 2002; Bah et al. 2004; Shuang et al. 2004; Strutz-Seebohm et al. 2006; Dutta et al. 2007; Han et al. 2010). To prevent serious side effects of KA receptor-modulating medicines these processes and effects should be investigated with caution.

KA receptors, and especially the GluK2 subunit and maybe GluK3, might be interesting targets for enhancing cognition. However, lots of research still needs to be done before compounds acting on these receptors can be used for this purpose. There is still a lot of controversy about the location and involvement of the different subunits at various synapses. More specific knock-out studies should investigate the role of the different subunits in synaptic plasticity and cognition. During these studies and studies which specific compounds there should be a close watch on possible side effects like epilepsy, perception changes or symptoms of one of the diseases described above. For the enhancement of cognition without a pathological reason fewer side effects will be tolerated than in research studying diseases like epilepsy.

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Supplement

Table 2: Expression of subunits and heteromeric KA receptors in the adult brain

Receptor	Brain structure	Region
GluK1	Cerebellum	Purkinje cell layer [6,7]
	Cerebral Cortex/Neocortex	Cingulate gyrus, EC, Piriform cortex, Sensory cortex [6,7]
	Hippocampus	CA1, DG, Sb [6,7]
	Pons	Lateral Superior Olive [8]
	Septum [7]	
	Thalamus [7]	Anteroventral thalamus [6]
	Trigeminal subnucleus caudalis	Substantia gelatinosa [9]
GluK2	Basal ganglia	Caudate Putamen [6,7]
	Cerebellum	Granule cell layer [6,7]
	Cerebral Cortex	Cingulate gyrus, Piriform cortex, EC [1,7]
	Hippocampus	CA1, CA3, DG [1,6,7]
	Olfactory lobe [1]	
GluK3	Amygdala	Anterior amygdaloid area [5]
	Basal ganglia	Caudate Putamen [6,7]
	Cerebellum	Stellate/basket [6,7]
	Cerebral Cortex	Layers I, VI, V; Cingulate gyrus, EC [3,7]
	Hippocampus	CA3 (SL), DG, Sb [3,5-7]
	Hypothalamus	Ventral medial hypothalamic nucleus [6]
	Midbrain [3]	
	Olfactory lobe	Anterior olfactory nucleus [5]
	Pons	Pontine nuclei [6]
	Septum [7]	
	Thalamus [7]	Reticular thalamic nucleus [2,3,5,6]
GluK4	Anterior commisure [6]	
	Cerebellum	Purkinje cell layer [6,7]
	Cerebral Cortex [6]	EC
	Corpus Callosum [6]	
	Hippocampus	CA3, DG, Sb [4,6,7]
GluK5	Basal ganglia	Caudate Putamen [4,7]
	Cerebellum	Granule cell layer [4,6,7]
	Cerebral cortex/Neocortex	Cingulate gyrus, EC, Piriform Cortex [4,6,7]
	Entorhinal cortex	
	Hippocampus	CA1, CA3, DG [4,6,7]
	Hypothalamus	Medial preoptic, suprachiasmatic and ventral medial hypothalamic nuclei [6]
	Medial habenula [4]	
	Pineal Gland [6]	
	Septal nuclei	BNST, DR, LC [6]
	Septum [7]	
	Thalamus [7]	

[1]: (Egebjerg et al. 1991), [2]: (Werner et al. 1991), [3]: (Bettler et al. 1992), [4]: (Herb et al. 1992), [5]: (Lomeli et al. 1992), [6]: (Wisden et al. 1993), [7]: (Bahn et al. 1994), [8]: (Vitten et al. 2004), [9]: (Park et al. 2010),
BNST, Bed nucleus of the stria terminalis; DG, Dentate gyrus; DR, dorsal raphe; EC, Enthorhical Cortex; LC, locus coeruleus; Sb, subiculum; SL, Stratum lucidum