The discovery of GluA3-dependent synaptic plasticity

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Chapter 5:

Summary and general discussion

Most excitatory neurons in our brain express three different types of AMPAR subunits: GluA1, GluA2 and GluA3. Whereas GluA1 and GluA2 have been extensively studied in the past 25 years, GluA3 has been largely ignored, and at the start of my PhD virtually nothing was known about this forgotten subunit.

In this thesis I present "The discovery of GluA3-dependent synaptic plasticity".

I found that an emotional event leads to a massive synaptic potentiation in the hippocampus through the activation of GluA3. In addition, GluA3 in the cerebellum is crucial for motor learning. And finally, without GluA3 a mouse is resistant to Alzheimer-related symptoms.

5.0) Summary

In **Chapter 1**, I review the basis of synaptic plasticity and its relation with learning and memory. I give a brief description of the brain structures under study in this thesis, namely the hippocampus and cerebellum. Furthermore, I introduce glutamate receptors, and specifically AMPA receptors. Finally, I describe the basic characteristics of Alzheimer's disease and the known effects of amyloid β on glutamate receptors.

In **Chapter 2** we aim to acknowledge the historically neglected GluA3 subunit. In CA1 pyramidal neurons of the hippocampus, two types of AMPARs predominate: those that are composed of heteromers of GluA1 and GluA2, and those containing heteromers of GluA3 and GluA2. Years of extensive study have revealed that GluA1-containing AMPARs play a main role in LTP and memory formation. In contrast, GluA3-containing AMPARs have been largely overlooked, likely because, in the absence of GluA3, basal synaptic transmission, LTP and memory formation remain largely unchanged. In this chapter, we reveal that GluA3-containing AMPARs are inactive and contribute little to synaptic currents under basal conditions. However, we find that upon a fearful experience GluA3 channel function is restored through a rise in intracellular cAMP levels driven by norepinephrine release. This restoration of GluA3 function leads to a massive and transient potentiation that does not require trafficking of receptors, but rather changes in single channel conductance.

Chapter 3 explores the role of GluA1- and GluA3-containing AMPARs in LTP and procedural memory in the cerebellum. In this chapter we show that LTP at the parallel fiber to Purkinje cell synapse do not depend on GluA1-, but do depend on GluA3-containing AMPARs. This form of LTP involves changes in single channel

conductance mediated by an increase in cAMP and subsequent activation of Epac2. Furthermore, GluA3 is required for the adaptation of the vestibulo-ocular reflex, suggesting that GluA3-plasticity in Purkinje cells is crucial for motor learning.

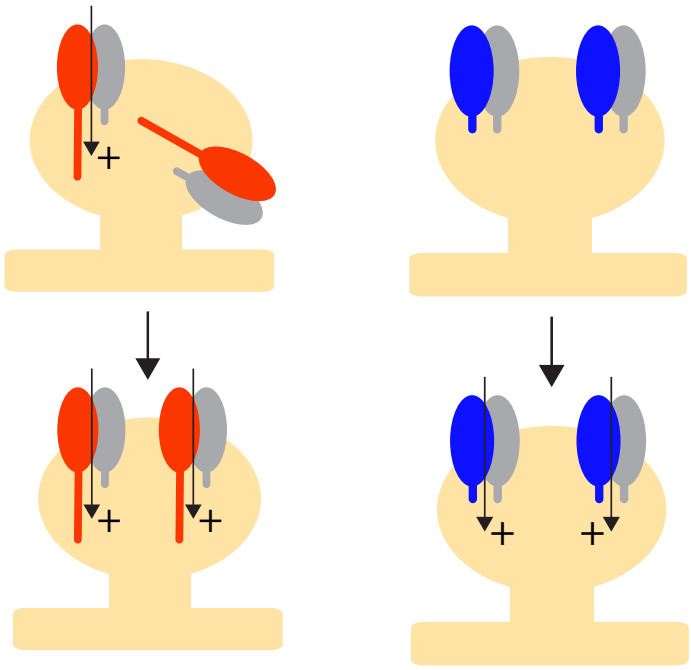
	GluA1-containing AMPAR	GluA3-containing AMPAR
C-tail	Long	Short
State under basal conditions	Open / Active	Closed / Inactive / Dormant
Necessary for LTP	Yes	No
Trafficking	Activity-dependent	Activity-independent / constitutive
Plasticity mechanism	Insertion into the synapse	Opening / activation
Model scheme upon synaptic plasticity		
Involved in memory formation	Yes	No

Table 1: Overview of differences between GluA1- and GluA3-containing AMPARs in the hippocampus. GluA1 subunit in red, GluA2 subunit in grey, GluA3 subunit in blue.

In **Chapter 4** we return to the hippocampus to study how the GluA3 subunit is implicated in Alzheimer's disease. Experiments in AD mouse models have shown that soluble oligomeric clusters of Aβ trigger synaptic weakening, a loss of synapses and a reduction in synaptic plasticity. We find that neurons lacking GluA3 are resistant to Aβ-mediated synaptic transmission of AMPAR and NMDAR currents, and Aβ oligomers are only capable of blocking LTP in neurons expressing GluA3. In addition, APP/PS1 mice, a mouse model for familial Alzheimer's, do not show spine loss, do not have memory impairment, and do not show premature mortality when they lack GluA3. Altogether these results suggest that the expression of synaptic and cognitive deficits mediated by Aβ require the presence of GluA3.

5.1) The role of GluA3-plasticity in the hippocampus

In **Chapter 2**, we have uncovered a new type of synaptic plasticity in the hippocampus that depends on GluA3. However, we found no evidence showing that the newly discovered GluA3-dependent plasticity contributes to memory formation, at least in the paradigms we tested. Thus, memory formation appears to depend on GluA1-plasticity, and not on GluA3-plasticity. Previously, the role of GluA3 hasn't been a focus in research, but in light of the information presented in this thesis the topic becomes much more relevant, even more since the absence of GluA3 protects against the synaptotoxic effects of Aβ. It is intriguing to speculate: what could be the role of GluA3-containing AMPARs in the hippocampus?

5.1.1) Synaptic replacement

There is indirect evidence showing that AMPARs composed of heterodimers of GluA2 and GluA3 may replace GluA1/2-AMPARs in an activity-independent manner in slice cultures in the hippocampus (Shi et al., 2001). In this paper, a mutated form of GluA2 was used, GluA2(R586Q)-GFP, that is inwardly rectifying. GluA2(R586Q)-GFP homomers are continuously delivered to the synapse replacing existing AMPARs, which was observed by an increase in rectification while leaving synapse strength unaltered. When co-expressing GluA2(R586Q)-GFP and GluA3 they observed again inward rectification, suggesting that GluA2/3-AMPARs behave as GluA2/2-AMPARs. They expressed GluA3-GFP in neurons and found that they went into spines, without rectification and resulting in depressed synaptic transmission. At that time, it was unclear how to interpret this result. However, in light of the recent

results presented in **Chapter 2**, a simple explanation can be proposed. When GluA3-GFP is expressed, GluA3/3 homomers cannot be formed (Coleman et al., 2016), but instead GluA3-GFP forms heteromers with GluA2. These GluA2/3-AMPARs go into spines and synapses replacing AMPARs, and cause synaptic depression since they are in an inactive state. The inward rectification observed upon co-expression of GluA2(R586Q)-GFP and GluA3 can be derived from recombinant GluA2 homomers trafficking, since GluA2/3-AMPARs would be in an inactive state.

Activity-independent synaptic AMPAR exchange occurs *in vivo* with a rate time constant of around 20 hours (McCormack et al., 2006; Takahashi et al., 2003). It was hypothesized that this constitutive process could contribute to the stabilization of memories, as a molecular mechanism for consolidation of encoded memories (Kessels and Malinow, 2009). If this were the case, GluA3-containing AMPARs would be necessary for the stabilization of memories. Therefore, we would expect GluA3-deficient mice to have less stable memories. However, in **Chapter 2** we did not find evidence supporting this hypothesis: our results show that long-term fear memories are present in GluA3-deficient mice (at least up to one month after fear conditioning), and freezing levels are even slightly higher in these mice compared with wild-type littermates. These results seem conflicting with a model in which GluA3 is important for the consolidation of contextual fear memories.

AMPAR replacement is still a possible feature of GluA3-containing AMPARs, but about its function I can only speculate. The constitutive replacement occurs without a change in synaptic strength, which in light of our findings would entail a replacement of constitutively active GluA1-containing AMPARs by GluA3-containing AMPARs in an open state. However, when GluA3-containing AMPARs become inactive, then synaptic strength would be reduced upon this process, and the memory potentially weakened. In this scenario, GluA3-plasticity may function to sharpen a memory during arousal when norepinephrine levels are high.

5.1.2) Information flow enhancement

GluA3-plasticity is likely a selective feature of excitatory neurons, since most inhibitory neurons in the hippocampus lack GluA2/3-AMPARs (Leranth et al., 1996), although it has been reported that GluA3 is expressed in particular in parvalbumin interneurons in the visual cortex of monkeys (Kooijmans et al., 2014) and in a subset of PV neurons in the hippocampus of rats (Moga et al., 2003). However, the hippocampal PV neurons do not express GluA2, and since GluA3 obligatory exist in

an AMPAR configuration of GluA2/3 heteromers (Coleman et al., 2016), it remains to be established what the role of GluA3 in these interneurons may be.

GluA3-plasticity does not appear to be specific of a subset of neurons upon for instance fear conditioning, i.e. it occurs in a vast population of excitatory neurons (as we found that all the recorded CA1 neurons under high cAMP level conditions showed increased synaptic strength). A function of this plasticity that occurs massively and in excitatory neurons could thus be to enhance information flow during an emotional experience. This hypothesis may be in line with previous observations that GluA3-deficient mice display an increased aggressive behavior, since it points to a correlation between the presence of GluA3 and the control of emotional behavior (Adamczyk et al., 2012). GluA3-deficient mice also show a decreased delta and theta power during sleep compared with wild types (Steenland et al., 2008). Furthermore, preliminary results from our laboratory obtained by local field potential recordings in the hippocampus suggest that the activation of GluA3-plasticity is expressed by a desynchronization in slow wave theta-oscillations.

5.1.3) Adaptive behavior

It is also possible that GluA3 has a role in adaptive behavior, where the animal has to learn to respond to a change of rules. It would be interesting for example to evaluate whether extinction of a conditioned fear memory is affected in GluA3-deficient mice. Behavioral flexibility is the ability to change behavior patterns in response to a changing environment. Cognitive flexibility requiring set-shifting involves the medial prefrontal cortex, and it has been proposed that the trigger for abrupt changes in the network dynamics of this brain region, which occur when the animal has to respond to a change of rules, could be norepinephrine (Karlsson et al., 2012). This is especially interesting considering the effects of norepinephrine on GluA3-plasticity presented in this thesis. It is tempting to speculate that processes like behavioral flexibility and memory reconsolidation (Karlsson et al., 2012; Morice et al., 2007), which depend on norepinephrine or dopamine (neurotransmitters that lead to an increase in cAMP), may involve GluA3-dependent plasticity. Both processes require and "uncertainty phase" during which an old strategy or memory can be modified.

5.1.4) Functions mediated by other triggers

As we have found in **Chapter 2** of this thesis, norepinephrine through β-adrenergic receptor activation triggers GluA3-plasticity in the hippocampus, but it is not

necessarily the only trigger. Other neurotransmitters that produce a change in cAMP levels like dopamine or serotonin might also cause GluA3-plasticity. If this were the case, it would be intriguing to evaluate whether GluA3-plasticity is involved in cognitive or emotional processes mediated by these other neurotransmitters. Likewise, a future direction of research related with GluA3-plasticity could be to examine whether it is present in other brain structures.

Whereas we have not yet found a role for GluA3-containing AMPARs in hippocampus-related learning, we have discovered that in the cerebellum this AMPAR subunit plays a principal role in vestibulo-cerebellar motor learning. Further characteristics differentiating GluA3-plasticity between the hippocampus and cerebellum are discussed below (see section 4.3).

5.2) Susceptibility of GluA3-containing synapses to amyloid β

We do not know yet what the physiological/behavioral function of GluA3-containing AMPARs in the hippocampus is, but one of the remarkable findings contributing to the significance of GluA3 is that it makes synapses susceptible to amyloid-β (Aβ). In **Chapter 4** we have found that GluA3-containing AMPARs play a central role in Aβ-induced synaptotoxicity. It is possible that GluA3 is a direct target of Aβ, but we consider the possibility that Aβ hijacks an endogenous signaling pathway that eventually leads to the selective removal of GluA3-containing AMPARs from synapses. We propose a model where Aβ oligomers bind one or more surface receptors, thereby facilitating an endogenous NMDAR-dependent LTD-like signaling cascade that involves the recruitment of PICK1 (Kim et al., 2001; Terashima et al., 2008), ultimately leading to the selective removal of GluA3-containing AMPARs from synapses. PICK1 is an adaptor protein that selectively interacts with GluA2 and GluA3, and is involved in AMPAR endocytosis (Kim et al., 2001; Terashima et al., 2008). PICK1-deficient neurons were shown to be insensitive to Aβ-mediated synaptic depression (Alfonso et al., 2014). In this scenario, the removal of GluA3-containing AMPARs is a crucial step in the expression of Alzheimer's disease (AD) -related cognitive symptoms.

Something that has not been explored in this thesis is the relationship between the effects of Aβ on synapses and GluA3-plasticity. We have established in **Chapter 2** that GluA3-containing AMPARs can be in an open/active and closed/inactive state.

AD-symptoms may be more prevalent upon GluA3 activation. It also remains to be studied whether Aβ affects GluA3s equally in all its states or if one state of GluA3 renders it more sensible.

5.3) Distinct characteristics of GluA3-plasticity in the hippocampus and cerebellum

In **Chapter 2** and **Chapter 3** we have found and described for the first time GluA3-dependent synaptic plasticity in the hippocampus and cerebellum respectively. This process shares important properties in the two brain structures under study. In both cases, increased levels of cAMP lead to the activation of GluA3-plasticity. In response to a rise in cAMP, a large increase in the open-channel probability of GluA3-containing AMPARs is measured in both CA1 neurons and Purkinje cells. Thus, the properties of the membrane channels are modified, without evidence of trafficking of receptors to the surface. It is interesting to note, however, that some properties of GluA3-dependent plasticity are different in the hippocampus and cerebellum.

Although an increase in cAMP is the signal that triggers GluA3-plasticity, the trigger for cAMP itself has not been proven to be the same in both structures. In the hippocampus we have established that β-adrenergic receptor activation linked to adenylyl cyclases is a trigger for cAMP increase and GluA3-plasticity. In our case of study β-adrenergic receptor activation is caused by exposure of mice to a fearful experience or by a systemic epinephrine increase that in turn elevates norepinephrine levels. We predict that other signaling pathways that lead to an increase in cAMP levels, like dopamine or serotonin, could also trigger GluA3-plasticity. On the other hand, in the cerebellum the signal causing the rise in cAMP remains to be elucidated. It is known that small increases in Ca^{2+} concentration following parallel fiber stimulation can induce LTP. It would be interesting to study how these Ca^{2+} signals in Purkinje cells are transduced into adenylyl cyclase activation to increase the levels of cAMP. A possible candidate is the calcium/calmodulin-dependent adenylyl cyclase Adcy1 (Masada et al., 2012). Other candidates include orexin receptors, pituitary adenylyl cyclase-activating polypeptide receptors and norepinephrine. Although it is tempting to speculate that the latter is causing the cAMP increase as it happens in the hippocampus, it is questionable that an emotionally aroused state induced by norepinephrine would be consistently

needed for motor memory formation.

	Hippocampus	Cerebellum
cAMP dependent	Yes	Yes
PKA dependent	No	No
Epac dependent	No	Yes
Involves trafficking	No	No
Increased open-channel probability	Yes	Yes
Necessary for LTP	No	Yes
Trigger for cAMP increase	β-adrenergic receptor activation	To be determined
Effect on memory formation	No effect	Large effect

Table 1: Comparative overview of GluA3-dependent synaptic plasticity in the hippocampus and cerebellum (cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; Epac: exchange factor directly activated by cAMP; LTP: long term potentiation).

The mechanism of action of cAMP also differs between hippocampus and cerebellum. In the cerebellum, we have found that cAMP promotes the activation of GluA3 plasticity through Epac, the cAMP-regulated GEF for Rap1. On the contrary, we found that Epac is not the target of the cAMP increase in the hippocampus. furthermore it has been shown that strong, long lasting pharmacological activation of Epac leads to destabilization and loss of spines in the hippocampus, causing synaptic depression (Woolfrey et al., 2009). In line with this, Rap1 also causes synaptic depression, not potentiation (Huang et al., 2004; Zhu et al., 2002). Moreover, cAMP is not causing GluA3-plasticity through PKA or HCN channels, which are common effectors, and cAMP does not act directly on GluA3. We did find however that a farnesyl transferase inhibitor that blocks the activity of Ras-like proteins reduces GluA3-plasticity in this brain structure. Ras is a member of the superfamily that includes as well Rap1. Ras has been implicated in a variety of

cellular processes, including synaptic plasticity and AMPAR trafficking (Qin et al., 2005; Zhu et al., 2002). In this context, it is interesting to note that a novel interplay between cAMP and Ras has recently been reported: in rat sensory neurons Epac acts through activation of Ras rather than Rap1 (Shariati et al., 2016). It remains to be further studied whether GluA3-plasticity in the hippocampus could be mediated by a cAMP-regulated GEF for a member of the Ras family.

Another striking difference between the two brain structures under scrutiny relates to the state of GluA3-containing AMPARs under basal conditions. Whereas we saw that the absence of the GluA3 subunit has no effect on basal synaptic transmission in the hippocampus, it reduced transmission to 50% in Purkinje cells of the cerebellum. This may be because in Purkinje cells GluA3 are already partly active under basal conditions. However, it may be more likely that a change in basal transmission is the result of a lack of LTP. In Purkinje cells GluA1 does participate in synaptic currents, but in its absence basal transmission and LTP are not affected. Similarly, in the hippocampus, GluA1 is essential for normal basal transmission as well as LTP, whereas GluA3-containing AMPARs are not crucial for LTP and their absence does not affect basal transmission.

5.4) Future directions

The present thesis has described for the first time a major type of synaptic plasticity that depends on AMPAR subunit GluA3. This plasticity requires an increase in cAMP levels and it occurs through a change in open channel probability without trafficking of the receptor to the surface. As with any novel and exciting discovery, a new field of research presents itself with many questions and possibilities to explore.

As mentioned earlier, it remains to be established what is the role of GluA3-plasticity in the hippocampus, where it is triggered upon a fearful experience. Furthermore, is GluA3-plasticity present in other brain regions besides the hippocampus and cerebellum? This may be very likely, since GluA3 is expressed in most brain regions. If so, what role does this plasticity play in these structures? Can other neurotransmitters, besides norepinephrine, be triggers for the rise in cAMP that generates GluA3-plasticity? What is the target of cAMP in the hippocampus? Does Aβ differentially GluA3 in its active and inactive form?

We have found that GluA3-plasticity involves opening of the receptors upon an

increase in cAMP levels. But how is this process regulated? How long does the receptor stay active? Is there a mechanism for closure of the receptors, or are they recycled and replaced by receptors in an inactive state? In **Chapter 2** acute slices are prepared after the mouse has been through a fearful experience and cAMP levels increase in vivo; mEPSCs are recorded from these slices for hours, and until the end of the day recordings show increased mEPSC frequencies. Therefore, we hypothesize that there has to be an active regulatory mechanism to return the receptors to an inactive state, which does not occur once the brain is isolated and the slices are prepared. An unlikely alternative is that cAMP levels remain high in the slices throughout the day. It will be interesting thus to study through which process GluA3-containing AMPAR transmission returns to basal levels. For example, activation of cholinergic muscarinic receptors leads to a decrease in cAMP through G_i class GPCR, and receptors type m_1, m_2 and m_4 are present in the hippocampus (Buckley et al., 1988; Levey et al., 1991).

It would be interesting as well to decipher which parts of GluA3 are critical for plasticity. For example, using point mutations in the sequence of the protein could allow us to resolve which amino acids are interacting with the cAMP effector molecule triggering the putative conformational change that generates the change in single channel conductance of GluA3. In fact, GluA3 has unique structural features compared with other AMPAR subunits. In particular, its N-terminal domain is exceptionally large and motile (Sukumaran et al., 2011), a feature that may underlie the observed changes in open probability, or it could be the target of allosteric modulators. Moreover, it has recently been shown with x-ray crystallography and cryogenic electron microscopy that GluA2/3 heteromeric AMPARs can access multiple conformations. The structure of GluA2/3-AMPARs in particular deviates from the classical structure of AMPARs and resembles more that of NMDARs (Herguedas et al., 2016).

With this thesis, GluA3 may have finally reached the spotlight is deserves. I consider the work presented in this thesis as the first steps into a novel field of research related to AMPA receptors, their plasticity and function. There are many new questions about GluA3, surely more than there were before starting this work. Their answer in the future will shed more light into the functioning of the brain and hopefully help in the treatment of diseases as Alzheimer's disease.

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