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Title: Synaptic NF-kappa B pathway in neuronal plasticity and memory.

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Abstract: Several transcription factors are present at the synapse, and among these are the Rel-NF-kappa B pathway components. NF-kappa B is a constitutive transcription factor, with a strong presence in the brain of which a considerable part is located in the neuropiles.
This localization of the transcription factor, plus evidence pointing to different functions, is what gave place to two general hypotheses for synaptic NF-kappa B: a) The transcription factor plays a role in the synapse to nucleus communication, and it is retrogradely transported from polarized localizations to regulate gene expression; b) The transcription factor modulates the synaptic function locally. Evidence indicates that both mechanisms can operate simultaneously; here we will present different possibilities of these hypotheses that are supported by an increasing amount of data. We pay special attention to the local role of the transcription factor at the synapse, and based in the described evidence from different animal models, we propose several processes in which the transcription factor may change the synaptic strength.

February 21, 2014

Journal of Physiology - Paris Editors:

Please find enclosed our manuscript entitled **"Synaptic NF-kappa B pathway in neuronal plasticity and memory."** submitted to be published in the Journal of Physiology - Paris.
We believe that our paper is a valuable addition to the scientific literature reviewing, the presence and function of synaptic NF-kappa B at the synapse. We present the evidences of membrane localization for the transcription factor and a local role at this site. Several publications, including ours, have shown than NF-kappa B is necessary for neural plasticity and long-term memory consolidation. Typically NF-kappa B is activated during learning and translocates to the nucleus. This work aims to elucidate the dynamics and role of the transcription factor at the synapse during plasticity.
Authors have no conflict of interest to declare.
We request this manuscript to be considered as a Review article.

Thanks for your consideration.

Yours sincerely,

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The concerns from both reviewers where taken in account, in this resubmission.
Reviewer #1:

1) The MS should be checked for grammar. I have found a few errors in the introduction.
The grammar errors where corrected.

2) The second and third paragraphs of the introduction are very difficult to read and should be rephrased.
Second and third paragraphs where rephrased.

3) The idea that NF-kappa B acts directly on the synapse comes, according to the authors, from studies done in Drosophila in which Dorsal and Cactus proteins are required for glutamate receptor clustering at the NMJ. They compare this process to the AChR clustering in mice that requires Rapsyn. Rapsyn is regulated by NF-kappa B, but at the transcriptional level, so it is not clear to me how these two processes are related. It seems that, in mammals, most synaptic effects of this transcription factor can be explained by NF-kappa B regulation of transcription rather than direct interaction with membrane or scaffolding proteins. However, if this is not the case, the authors should clarify the evidence that supports their hypothesis more clearly.
The drosophila results point to a local role of the transcription factor and the experiments performed in mammal cells indicate an incidence thru transcription but without ruling out the local role. We clarified this point.

Reviewer #2: The review by Salles et al. outlines the pivotal roles of the NF kappa B signaling pathways, principally those related to the process of memory formation. One of these roles is associated with its translocation to the nucleus, where it transduces synaptic activity in the transcriptional induction of specific genes, regulating gene expression. Besides, the authors suggest that this transcription factor can modulate the synaptic changes locally, for instances changing the synaptic strength by affecting AMPA receptors at the membrane or by changing the presence of diverse synaptic proteins. These roles are not mutually exclusive and can act independently. The authors present evidence for both roles. In fact, NF kappa B may participate, following its activation, in the synaptic and the structural plasticity associated with the consolidation of long-term memories. Overall, this manuscript is well written and appears relevant for a better comprehension of the role of the NF kappa B signalling pathway in a number of functional processes, including learning and memory. Finally, this study has a significant interest for the scientific community related to the molecular mechanisms associated with memory formation.
There is a growing body of evidence showing that similar mechanism, at least some of them, are involved in other memory phases such reconsolidation and extinction. Taking into account that the authors emphasized the involvement of this transcription factor in memory formation, some discussion concerning a hypothetical role of NF kappa B signalling pathway in these memory processes besides consolidation would be useful.
The role of the NF-kappa B pathway in the memory phases is described in the introduction, and the possible role of the synaptic NF-kappa B in the memory phases is discussed in the discussion.

Highlights (for review)

- NF-kappa B is present at the synapses.
- After activation NF-kappa B can retrogradely be transported to the nucleus.
- NF-kappa B may also have a local role at the synapses.
- Synaptic NF-kappa B translocates to the membranes during memory consolidation.
- Local NF-kappa B may recruit post-translational modifying proteins.

Synaptic NF-kappa B pathway in neuronal plasticity and memory.

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Keywords

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Abstract

Several transcription factors are present at the synapse, and among these are the Rel-NF-kappa B pathway components. NF-kappa B is a constitutive transcription factor, with a strong presence in the brain of which a considerable part is located in the neuropiles.

This localization of the transcription factor, plus evidence pointing to different functions, is what gave place to two general hypotheses for synaptic NF-kappa B: a) The transcription factor plays a role in the synapse to nucleus communication, and it is retrogradely transported from polarized localizations to regulate gene expression; b)

The transcription factor modulates the synaptic function locally. Evidence indicates that both mechanisms can operate simultaneously; here we will present different possibilities of these hypotheses that are supported by an increasing amount of data. We pay special attention to the local role of the transcription factor at the synapse, and based in the described evidence from different animal models, we propose several processes in which the transcription factor may change the synaptic strength.

Introduction

Several transcription factors have been reported in dendrites: NF-kappa B, Creb, Stat3 and ELK-1 (Kaltschmidt et al., 1993; Murata et al., 2000; Sgambato et al., 1998; Suzuki et al., 1997, 1998). Among these, NF-kappa B has been reported in axon (Mindorff et al., 2007; Sulejczak and Skup, 2000; Povelones et al., 1997) and dendrites (Boersma et al., 2011; Heckscher et al., 2007; Kaltschmidt et al., 1993; Guerrini et al., 1995; Meberg et al., 1996; Suzuki et al., 1997). In the dendrites this transcription factor has being reported in close relation with post-synaptic densities (Boersma et al., 2011; Suzuki et al., 1997).

The Rel/NF-kappa B transcription factor family is a dimer that can be composed in vertebrates by seven proteins: Rel A/p65, c-Rel, RelB, p100, p52, p105 and p50 (Baldwin, 1996; Ghosh et al., 1998), and in invertebrates by three: Dorsal, Dif (dorsal related immunity factor) and Relish (Hetru and Hoffmann, 2009). The prototypical dimer is formed by two subunits; p65 and p50 (May and Ghosh 1997). In vertebrates, NF-kappa B is mostly found in the cytoplasm bound to a regulatory protein that inhibits it, I kappa B (IkB): IkBα, IkBβ, IkBε, y Bcl-3 (Whiteside and Israël, 1997). In invertebrates this inhibitory component is the protein Cactus (Roth et al., 1989). Upon

activation, IkB is phosphorylated by the IkB Kinase (IKK, composed of IKK α, β and γ, also called IKK1, IKK2 and NEMO, respectively), ubiquitinated and degraded by the 26S proteasome leaving the remaining dimer free (Karin and Ben-Neria, 2000). This exposes the nuclear localization signal (NLS) and the DNA binding site of the TF, and is usually considered as active NF-kappa B, because it is able to bind DNA and promote transcription (Baeuerle and Baltimore, 1988). Recent evidences indicate that the regulation of the pathway is much more complex, for example p65 and p50 are the targets of many other post-translational modifications such as ubiquitination, acetylation, methylation, phosphorylation, oxidation/reduction, and prolyl-isomerization (Toledano et al., 1993; Schmitz et al., 2004; Huang et al., 2010). NF-kappa B may selectively target different genes due to site-specific phosphorylations of the p65 subunit (Hochrainer et al., 2013). The post-translational modifications on NF-kappa B change its transcriptional activity by directly affecting its capacity to interact with the DNA or indirectly by affecting protein-protein association of NF-kappa B (Zhong et. al 1998, Chen et al., 2005; Huang et al., 2010; Hochrainer et al., 2013).

Among the protein-protein regulation exerted by post-translational modifications on NF-kappa B is the phosphorylation of the transcription factor that leads to the recruiting of enzymes to particular localizations, a process observed in engaging acetyltransferases to particular promoters in the chromatin (Zhong et al., 1998).

This transcription factor is present in most mammalian cell types including neurons and glia (Kaltschmidt et al. 1994; Sparacio et al., 1992). NF-kappa B is conserved across different Phyla, and has been found in the nervous system of species such as flies, crabs, mice and humans (Meffert and Baltimore, 2005; Gilmore and Wolenski, 2012).

The activation of nuclear NF-kappa B has been associated with long-term synaptic plasticity and the consolidation of long-term memory (LTM) (Freudenthal and Romano,

2000; Kaltschmidt and Kaltschmidt, 2009; Meffert et al., 2003; Romano et al., 2006; Snow et al., 2013). This transcription factor is activated during long-term potentiation (LTP) in the mouse hippocampus (Freudenthal et al., 2004) and an increment in the NF-kappa B dependent gene p50 is observed (Meberg et al., 1996). Treatment of mouse brain slices with a DNA decoy containing the consensus sequence recognized by NF-kappa B, prevented the induction of long-term depression and reduced the magnitude of LTP (Albensi and Mattson, 2000).

In the same line of evidence, the NF-kappa B pathway of neuronal growth drives the gene expression observed 24 hours after LTP induction in the rat perforant pathway (Ryan et al., 2012). Accordingly, in the p50 knockout mice late-LTP is impaired in CA1 pyramidal cells (Oikawa et al., 2012) and the c-Rel knockout mice has reduced late LTP in the CA1Schaffer collaterals (Ahn et al., 2008).

A strong regulation of nuclear NF-kappa B DNA binding activity is found during LTM consolidation, reconsolidation and extinction of crabs, mice and rats (Freudenthal et al., 2005; Merlo et al., 2002; O'Sullivan et al., 2007; Merlo and Romano, 2008; de la Fuente et al., 2011). The inhibition of the IkB phosphorylation with sulfasalazine or the use of a double stranded DNA decoy with the kB consensus sequence to interfere with the chromatin interaction during consolidation and reconsolidation proves to be amnesic at testing in mouse and crab (Boccia et al., 2007; Freudenthal et al., 2005; Merlo et al., 2002).

This review does not intend to be comprehensive in the many functions of the NF-kappa pathway in the brain but to deal specifically with the local synaptic functions previously evidenced or suggested by the accumulated data.

Presence of NF-kappa B pathway proteins at the synapse

NF-kappa B at the synapse was first described by Kaltschmidt group in 1993 (Kaltschmidt et al., 1993) in rat nervous system. Specifically the p50 and its precursor p105 showed staining at retina, cortex and striatum synapses, and the inducible form of NF-kappa B was detectable by EMSA in cortex synaptosomes. Cerebellum cultures showed a strong immunostaining for p65 at the synaptic contacts (Guerrini et al., 1995). Furthermorethe p65/p50 dimer was identified usingsupershift of hippocampal synapstosomal proteins (Meberg et al., 1996).

Immunostaining of the NF-kappa B inhibitor IkB was detected at rat neuronal fibers (Joseph et al., 1996). Not long after, this finding was corroborated in the hippocampal and cortical synapses of the rat and the presence of both IkB-α and p50 was observed at the post-synaptic density by electron microscopy and EMSA (Suzuki et al., 1997). IkB-β was also found, in brain synaptosomes of mouse (Meffert et al., 2003).

In human neuromuscular junctions, p65 was abundant post-synaptically but not p50 (Yang et al. 1998). The localization of the transcription factor in the *Drosophila* neuromuscular junctions -both Dorsal and cactus were detected by immunochemistry (Cantera et al., 1999)-, suggests that the presence in synapse is conserved through Evolution. Recently the IKK complex (IKK α, β and γ) has been detected in the synaptosomal content and postsynaptic densities, altogether with Rel B and c-Rel that appears concentrated in the postsynaptic densities (Schmeisser et al., 2012).

One important finding regarding NF-kappa B localization at synapses is that mice with no p65 have no detectable NF-kappa B DNA binding activity at the synapse nor synaptic IkB presence, indicating that among all the NF-kappa B subunits, p65 is

probably the point of interaction of the transporting complex with the transcription factor for that localization (Meffert et al., 2003)

Several reports indicate also an axonal localization for components of the NF-kappa B pathway. Immunostaining for p65 has been reported in the neuronal fibers of rat (Sulejczak and Skup, 2000). The NF-kappa B signaling proteins p65 and IKK have been reported in the axon initial segment (AIS), and IKK was identified attached to microtubules (Schultz et al., 2006; Sanchez-Ponce et al., 2008). Some controversy rose about the presence of IkB in the AIS, strong recognition to an unidentified epitope was found in IkB knockout mice, and IkB seems not to be necessary for the AIS assembly (Buffington et al., 2012). NF-kappa B DNA binding activity is found also in the axoplasm of *Aplysia* (Povelones., et al 1997).

These findings indicate that all the necessary components of the NF-kappa B activation pathway are present in a variety of synapses and neural processes of very diverse animal models, evidencing the relevance of this pathway in that particular localization.

Transport of NF-kappa B like mRNA in neurons

Recently, RNA from cargo complexes associated with motor protein kinesin was shown to be required for the establishment of long-term facilitation in *Aplysia*.

A screening of RNAs in these complexes yielded p50-like mRNA as one of the identified sequences. This interaction points to the possibility that p50 is one of the RNAs that are actively transported to synapses during learning (Puthanveettil et al., 2013). The local translation of transcription factors in dendrites has been suggested to play a role in intracellular and intercellular communication (Eberwine et al., 2001).

One possibility is that different post-translational modification can occur in the dendrite versus the cell body, allowing a specific signaling associated with the protein origin (Barrett et al., 2006).

NF-kappa B is involved in synaptogenesis, synaptic reorganization and structural plasticity

A growing amount of reports point to a role of NF-kappa B signaling pathway in the regulation of structural changes observed in synaptic connections, both the shape and the regulation of spine density, in development stages and in the adult.

Dendritic changes in nucleus accumbens (NA) are associated with the behavioral sensitization to cocaine. The manipulation of the IKK activity using either a constitutively active or a dominant negative version of the protein, affect the number of dendritic spines in the mouse NA. The dominant negative version of IKK decreases the basal number of dendritic spines, blocks the increase seen by the administration of cocaine, and inhibits the rewarding effect of the alkaloid (Russo et al., 2009).

In mice the genetic ablation of the NF-kappa B pathway by the expression of an inducible superrepressor IkB, leads in the dentate gyrus (DG) to degenerating neurites, hampered axogenesis and synaptogenesis; while the reestablishment of the pathway is accompanied by a recovery of structural and behavioral defects (Imielski et al., 2012).

This suggests that NF-kappa B is implicated in controlling development, growth, guidance and branching of axons and dendrites. Moreover, in adults, the transcription factor has a role in regulating dendrite arbor size and complexity, and dendritic spine density (Gutierrez and Davies, 2011).

NF-kappa B controls excitatory synapse and dendritic spine formation and morphology in murine hippocampal neurons. During synapse development, loss of NF-kappa B

reduces spine density, but after developmental synaptogenesis stabilizes, endogenous NF-kappa B activity is low and p65 deficiency no longer attenuates basal spine density. In mature neurons activation of NF-kappa B by stimuli that induce and demand for new synapses, NF-kappa B is essential for up regulating spine density in response to these stimuli. Summarizing, NF-kappa B is imparting the transcriptional regulation required for the induction of changes to, but not maintenance of, excitatory synapse and spine density (Boersma et al., 2011).

In other reports inhibition of synaptic IKK activity resulted in a reduction of dendritic spines, reduced AMPA-mediated basal synaptic transmission, and interfered with spatial learning in adult mice (Schmeisser et al., 2012).

Activation of the IKK signaling pathways during social defeat is both necessary and sufficient to induce synaptic alterations and behavioral effects (Christoffel et al., 2011). This establishes a link between IKK related structural plasticity and behavior.

A variety of extracellular signals activate the signaling pathway of this transcription factor that either promotes or inhibits growth, depending on the IKK activity and the phosphorylation status of the p65 NF-kappa B subunit.

Increasing evidence indicates that structural behavior related dendritic spines and synapses rearrangement, are part of the enduring of the memory trace (Caroni et al., 2012). NF-kappa B, whose activation was already reported as taking part of the memory consolidation process, is a candidate to exert its control in governing these rearrangements.

These novel roles for NF-kappa B, together with recent evidence implicating NF-kappa B in the regulation of neurogenesis in the embryo and adult (Imielski et al., 2012;

Methot et al., 2013), have important implications for neural development and for learning and memory in the mature nervous system (Gutierrez and Davies, 2011).

NF-kappa B synaptic activation and dynamics

Although inducible NF-kappa B has been found in the synapses of various areas of mouse and rat brain, typically the physiological activation of the transcription factor *in vivo* (IkB interaction level or post-translational modifications) at the synapse has not been evaluated and instead the activation was estimated by the DNA binding activity in the nucleus. Very few reports studied the physiological processes that activate this pool of transcription factor at the synapse (Freudenthal and Romano, 2000; Meffert et al., 2003) or the modifications and localization changes that locally happen to it *in vivo*.

Nuclear NF-kappa B like DNA binding activity is enhanced immediately after training in the brain of the crab *Neohelice granulata* (=Chasmagnathus), after a spaced presentation protocol that induces LTM, but not in a massive presentation protocol that yields short term memory. At the same time, the synaptosomal DNA binding activity is also higher, suggesting that only the spaced presentation triggers the IkB degradation in both localizations (Freudenthal and Romano, 2000).

The specific NF-kappa B like DNA binding activity found in the axoplasm of Aplysia, rapidly decreases as a response to injury (Povelones et al., 1997).

In the *Drosophila* neuromuscular junction (NMJ), Dorsal and Cactus proteins that are Drosophila's NF-kappa B and IkB orthologs respectively, are both involved in the normal function of this synapse (Beramendi et al., 2005).

Several reports have identified both proteins in the post synaptic side of the neuromuscular junction of the fly (Cantera et al., 1999; Bolatto et al., 2003; Heckscher et al., 2007). Electrical stimulation of the nerves or incubation with glutamate (main neurotransmitter of the invertebrate NMJ), through calcium, decreases both proteins at the neuromuscular junction, indicating that synaptic activity regulates the transcription factor localization (Bolatto et al., 2003).

In mouse hippocampal cultures, synaptosomal NF-kappa B (p65/p50) activity was increased by depolarization, glutamate, and exposure to the Ca+ ionophoreionomicin. Ca+ chelation with EGTA indicate that the activation was dependent in local increments of intracellular calcium (Meffert et al., 2003).

Recently in our lab we described the NF-kappa B hippocampal dynamics during LTM consolidation in mice. First we described overall NF-kappa B pathway components distribution in mice hippocampal slices. The p65 dimer component was present in nucleus, perinuclear cytoplasm and dendrites of CA1 Pyramidal neurons. IkB is mostly found in dendrites and perinuclear cytoplasm. Finally, we found NF-kappa B activity in nucleus, cytoplasm and synaptosomes.

Using sequential synaptosomal fractioning, we have established that synaptosomal NF-kappa B is distinctly present in two pools. One pool is the NF-kappa B free in the synaptoplasm, and the other is strongly bound to synaptic membranes.

We found that synaptosomal NF-kappa B is activated during consolidation with a different time course than nuclear activation. NF-kappa B is activated 5 minutes post training at the synapse, and the nuclear activation occurs 45 minutes post training in the inhibitory avoidance paradigm in mice. Moreover, the NF-kappa B pathway

components p65 and IkB translocate to the synaptic membrane 5 minutes post training. This speaks of a system in which after training-related synaptic activation, NF-kappa B translocates to the membrane leaving a pool in the synaptoplasm. At the same time, the DNA binding activity indicates that is freed from IkB and able to be transported to the nucleus. The NF-kappa B translocation suggests a local role recruiting other proteins in situ or labeling and preparing dendrites for remodeling and synaptic plasticity, affecting memory consolidation (Salles et al., unpublished).

Retrograde transport

Since the discovery that NF-kappa B is present in dendrites, the principal hypothesis was that the transcription factor was able to be transported from the synapse to the nucleus, to transduce the synaptic activity in transcriptional activity. Several of these steps proved to be right. In rat hippocampal cultures, the stimulation with glutamate, kainite or depolarization, resulted in redistribution of p65 from neurites to the nucleus. This redistribution was dependent in a functional NLS, suggesting that active NF-kappa B was the transported subpopulation of the transcription factor (Wellmann et al., 2001).

Experiments in mice hippocampal cultures indicates that calcium elevation due to synaptic stimulation by N-Methyl-D-aspartate (NMDA), leads to NF-kappa B translocation to the nucleus. The subsequent NF-kappa B accumulation in the nucleus was dependent in Ca2+/calmodulin-dependent protein kinase II (CaMKII), and followed by an increment in IkB transcription, the prototypical promoter regulated by a kB consensus sequence (Meffert et al., 2003).

The dynein/dynactin motor complex mediates the transport of NF-kappa B to the nucleus along with microtubules, and this transport is mediated by the p65-NLS interaction with importinsα/β (Mikenberg et al., 2007).

A recent report indicate that huntingtin protein physiological function includes a role similar to importins, stimulating the transport of active NF-kappa B from dendrites to the nucleus (Marcora and Kennedy, 2010), thus suggesting that it may contribute to the etiology of Huntington Disease.

Taken together this data indicate that the NF-kappa B present at the synapse is capable of translocating to the nucleus upon local Ca++ raising synaptic stimuli, where it transduces synaptic activity in transcriptional induction of specific genes.

Recent unpublished observations from our lab indicate that during long-term inhibitory avoidance consolidation in mice, p65 and IkB α translocate to synaptosomal membranes (Salles et al., unpublished).

Role of NF-kappa B in receptor clustering and synaptic strength regulation

Reports from different animal models and synaptic plasticity paradigms indicate that NF-kappa B plays a role in defining the post-synaptic composition, and that this regulation is the basis of the synaptic strength.

Dorsal and cactus mobilization after neuromuscular junction (NMJ) activation through electrical or glutamate stimulation is mediated by calcium (Bolatto et al., 2003). Glutamate receptor clustering in the NMJ of drosophila is mediated by dorsal and cactus. Dorsal and cactus surround glutamate receptor clusters of the post synapses at the NMJ. The evidence described by Hecksher et al., supports the idea that dorsal and

cactus regulate the membrane insertion of glutamate receptors at the NMJ at a post-translational level (Heckscher et al., 2007).

At mouse NMJ, acetylcholine receptor (AChR) clustering is stimulated by agrin and requires several proteins, including AChR-associated scaffold protein rapsyn.

The selective deficiency of p65 in the skeletal muscle is followed by a reduction of AChR density at the NMJ and a decrement in the level of rapsyn. Thus, in mice at least part of AChR clustering is controlled through transcriptional regulation exerted by NF-kappa B over synaptic protein Rapsyn (Wang et al., 2010). The authors of this paper do not rule out a local effect at the synapse of the transcription factor besides its transcriptional involvement in receptor clustering.

In mouse, interference with the NF-kappa B signaling indicate that the pathway is directly involved in regulating the synaptic strength by affecting the presence of post-synaptic proteins like AMPA receptor subunit GluA1 density or membrane inclusion, and PSD-95 and Sap97 presence (O'Mahony et al., 2006; Boersma et al., 2011; Schmeisser et al., 2012; Mihalas et al., 2013).

These findings suggests that the NF-kappa B pathway is regulating receptor presence and clustering at the synapse.Evidence indicate that the transcription factor may be exerting its effects in a transcriptional dependent way a as well as locally at the synapse.

Conclusion and discussion

The data presented here point toward a regulatory role of the NF-kappa B signaling pathway in the synaptic changes observed after training induced plasticity, depolarization and neurotransmitter stimulation (Meffert et al., 2003; Meffert and

Baltimore 2005; O'Mahony et al., 2006; Boersma et al., 2011; Schmeisser et al., 2012; Mihalas et al., 2013).

Regarding the transcriptional activity of the synaptic NF-kappa B, is clear that the transcription factor is transported to the nucleus were it affects the transcription of target genes. This transcriptional activity itself could be differentially affected by somatic and synaptic transcription factor.

Learning related NF-kappa B activity in the nucleus after a LTM inducing protocol is shown to be biphasic with the first peak immediately after training and a second between 6 and 12 hours after training (Freudenthal and Romano, 2000). Both peaks of activity are necessary for memory consolidation (Merlo et al., 2002). One possibility is that the first peak is related to the somatic NF-kappa B, and the second to retrogradely transported transcription factor to the nucleus.

In inflammation, acute stimulation induces two distinct waves of NF-kappa B recruitment to target promoters, a fast recruitment to constitutively and immediately accessible promoters, and a late recruitment to promoters requiring stimulus-dependent modifications in chromatin structure to make NF-kappa B sites accessible (Saccani et al., 2001). This suggest the possibility that the two NF-kappa B activation peaks could be also affecting different gene pools in memory related processes and that the original localization of the transcription factor may be playing a role in this selection.

Evidence indicates that part of this regulation requires the transcriptional regulation exerted by NF-kappa B, both somatic and retrogradely transported to the nucleus from the synapse (see figure). But other evidence suggests that NF-kappa B has a local regulatory role at the synapse that is in part independent of transcription. As we propose that synaptic NF-kappa B may play a role in the definition of the mnesic trace, it is

logical to consider that this local role is involved in reconsolidation and extinction as well as in consolidation.

The research of Hecksher et al. (2007) is up to now the most convincing evidence for a local role of synaptic NF-kappa B (dorsal), regulating glutamate receptor density, in a transcriptionally independent way (see figure). Dorsal mutation decreases glutamate receptor II A at the NMJ. The data indicates that dorsal and cactus deficiencies, that typically have opposite effects (Govind, 1999) act through one pathway with similar effects in the glutamate receptor regulation.

Results from our laboratory (Salles et al., unpublished) indicate that in the inhibitory avoidance paradigm in mice, p65 and IkB α increase at synaptosomal membrane post-training. This translocation to membranes may recruit enzymes responsible of post-translational modifications to the post-synaptic densities (see figure). The recruiting in association with NF-kappa B signaling proteins has been shown for other localizations of the transcription factor. For example in the nucleus, upon binding to DNA, NF-kappa B is able to recruit acetyl-transferases and deacetyl-transferases to the promoters of the target genes and thus change the acetylation profile of chromatin (Zhong et al., 1998). At least one acetyl-transferase (ARD1) that has been described in dendrites -where it is involved in dendritic development- (Ohkawa et al., 2008) has been reported to interact with p65 in xenograft tumors and cancer cell lines (Xu et al., 2012).

It has been suggested that the ARD1-NAT1 complex has acetyltransferase activity against microtubules in dendrites (Ohkawa et al., 2008), and the possibility exist that this could affect the microtubules dynamics in order to reach dendritic spines (Doyle and Kiebler, 2011).

Exciting new evidence sheds light to the findings reported by Hecksher et al. (2007) and from Salles et al. on IkB proteins at the synapse. Recently the ribosomal protein S3, with a strong presence at dendrites (McCarthy and Milner, 2003), has been reported to directly interact with IkB in complex with p65 (Stanborough et al., 2014) posing the question if this could affect the translational equilibrium at dendrites.

Referring to a local role of the transcription factor, Boersma et al. (2011) reported that deficiency in p65 affected the synaptic strength through changes in AMPA receptor density in post-synaptic sites. A series of experiments with versions of p65 without transactivation domains (TA) or with DNA interacting amino acids R30 and R33 mutated suggest that the transcriptional activity of NF-kappa B is always required for the activity related changes. A possible interpretation is that the TA domains deleted covers the domains reported to interact with acetyl-transferases (Zhong et al., 1998), and the two mutated amino acids coincide with an important zone for the interaction with IkBα protein (Huxford et al., 1998 and Malek et al., 1998). The many relevant interactions exerted by NF-kappa B could be affected even in these two amino acid mutations. Preliminary data indicate that some mRNAs are co-precipitated with synaptic p65 (Freudenthal et al, unpublished), and during the aptamer screening of it, was clear that NF-kappa B is capable of binding RNA, with a similar structure as seen for DNA (Huang et al., 2003). This opens the possibility of the requirement of the DNA binding activity for non-transcriptional functions.

The NF-kappa B role in plasticity and memory is exciting an uncharted field with many facets to be explored (Boersma and Meffert, 2008; Snow et al., 2013). Altogether the data outlined here, plus some speculative ideas, leave open the possibility of a local role for NF-kappa B directly at the synapse.

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Figure Legend

This figure shows two post synaptic terminals in different states. In the lower one we can see the basal state of the spine where there is equilibrium between the different states and localizations of NF-kappa B. The TF can be free in the synaptoplasm with or without its inhibitor IkB and the NF-kappa B- IkB complex may or may not be attached to the membrane.

In the upper spine we can see that after synaptic activation, calcium channels open and can induce at least two different pathways of action for NF-kappa B. One pathway being the retrograde transport to the nucleus that involves activation of the TF by phosphorylation, ubiquitination and subsequent degradation of IkB by the proteasome 26 S. Further on the activated NF-kappa B dimmer binds to the Dynein/dynactin motors though the interaction with importing alpha and beta and is transported on the tubulin micotubules to the nucleus to promote transcription of target genes. And the other mechanism being the more novel one discussed in this review where the attachment of the NFkappa B/IkappaB complex to the PSD membranes increases and thus activates post-translational modification enzymes and receptor clustering.

p65 (NF-kappa B subunit), ABD (acetyltransferase binding domain), NLS (nuclear localization signal); p50 (NF-kappa B subunit); IkB (NF-kappa B inhibitor); ? (post-translational modifying proteins and other interacting proteins).

Figure(s)

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