

## **The Regulation of Synaptic Protein Turnover**

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## Abstract

Emerging evidence indicates that protein synthesis and degradation are necessary for the remodeling of synapses. These two processes govern cellular protein turnover, are tightly regulated, and neuronal activity modulates them in time and space. The anisotropic anatomy of the neurons presents a challenge for the study of protein turnover, but the understanding of protein turnover in neurons and its modulation in response to activity can help us to unravel the fine-tuned changes that occur at synapses in response to activity. Here we review the key experimental evidence demonstrating the role of protein synthesis and degradation in synaptic plasticity, and the turnover rates of specific neuronal proteins.

## Introduction

The human brain is composed of a trillion of neurons with complex and intricate arbors, that are interconnected by synapses (1). Synapses are highly dynamic in number and shape as a consequence of the continuous remodeling of neural circuits. A change in synaptic transmission elicited by neural activity is collectively called “synaptic plasticity”, and learning and memory rely, at least in part, on this process. Synapses are made up of proteins, including receptors for neurotransmitters, scaffolding molecules and signaling molecules. All proteins have a finite lifetime: they are synthesized and degraded continuously in order to maintain cellular function and viability. This continuous process is called “protein turnover”. But, why is protein turnover important for cells? Even when the cells are in a basal state, the protein pool is dynamic and the coordination between protein synthesis and degradation maintains a steady-state level of proteins that is constantly renewed (2). Protein turnover is not only important to maintain protein concentrations in the cell, but also to allow for changes. Modulation of the proteome is necessary for most cellular responses, involving modifications in general or specific protein turnover (3,4). Neurons also have the ability to modulate and adjust their proteome in response to specific cues, for example synaptic remodeling in response to

patterns of action potentials in neurons.

One complication of protein turnover in neurons is that synapses can be located up to hundreds of microns from the cell body. Where are proteins synthesized and degraded? Are proteins transported over the long distance from the soma to dendrites or axons? And if so, how do they reach their specific location within the intricate axonal and dendritic arbors. In fact, to overcome these challenges, neurons have very effective transport mechanisms to deliver proteins to remote regions of axons or dendrites, this have been recently reviewed in (5,6). Moreover, some proteins like receptors or scaffolding proteins are in continuous movement in and out of the synapse with rapid rates (reviewed in (7,8)). In addition to protein movement, neurons use local translation and degradation in dendrites and axons, allowing for a fine-tuned local protein turnover. Here we present an overview focused on the role of protein synthesis and proteasomal degradation, two main pathways controlling protein turnover, and how these two processes might work together to achieve neuronal plasticity. The role of autophagy in protein degradation is not discussed here due to space limitations.

## 1 Local computational and cell biological units

To understand the problem of regulating synaptic protein turnover in response to synaptic activity, it is necessary to know which neuronal locations process information and possess the machinery for protein turnover, and then study protein turnover within those regions.

Within dendrites, individual spines are the sites of excitatory synapses. Nevertheless, recent advances allowing for the stimulation of individual synapses have shown that dendritic branches and the associated synapses can be independently regulated by synaptic activity (9,10). Thus, the dendritic branch and its associated cluster of synapses may represent the fundamental computational unit for neurons. From this, one might predict that the turnover of some proteins changes only when needed by specific branches or an activated group of synapses within them. This is paralleled by

cell biological studies that have documented the localization of both the protein synthesis machinery and ubiquitin proteasome system component (UPS) in dendrites. In addition, recent high resolution *in situ* hybridization data indicate that mRNA molecules are distributed in local domains, along the proximal-distal dendritic axis (11). These data suggest a local sharing of protein synthesis and degradation machinery within the dendrite, giving to dendrite branches autonomy for the regulation of the protein turnover. Thus, to understand protein synthesis or degradation in response to neuronal activity the best approach would be to study separately the dendrites/axons and soma, and ideally study *in situ* the activated clusters of synapses in comparison with non-activated synapses. This approach is becoming more feasible with the advances in microscopy, protein labeling and local synaptic activation techniques.

## 2\_Local Protein Synthesis

The first evidence for dendritic translation in response to neuronal stimulation comes from the work of Feig and Lipton in 1993 (12). These authors applied electrical stimulation together with a muscarinic acetylcholine agonist (carbachol) to hippocampal slices and detected an increase in the incorporation of <sup>3</sup>H Leucine after 3 minutes, although there was no change in synaptic transmission. In 1996 Kang and Schuman discovered that local protein synthesis in hippocampal slices is necessary for synaptic plasticity induced by BDNF, and unlike other forms of plasticity BDNF-induced plasticity requires protein synthesis (13). These two pioneering studies have been supported by several others confirming the role of protein synthesis in plasticity, for example serotonin-induced facilitation (LTF, similar to long-term potentiation or LTP, in mammals) of sensory motor synapses in the marine mollusk *Aplysia californica* is protein synthesis-dependent (14), as well long-term depression (LTD) dependent of mGluR in hippocampal neurons (15). In addition, the blockade of spontaneous release of neurotransmitter by the presynaptic terminals induces translation in the postsynaptic terminal to enhance the responsiveness to the decreased input

(homeostatic plasticity) (16,17). Collectively, these studies provide strong evidence that protein synthesis can be modulated by various neuronal stimuli. The postsynaptic spine is biochemically isolated from the dendrite by the spine neck, and the molecular transport across the neck is restricted and modulated by neuronal activity (18). Within the relatively small volume of the spine, many chemical reactions take place including protein translation and degradation. Supporting the idea that proteins can be translated in spines, polyribosomes and smooth endoplasmic reticulum (SER), have been found in some spine heads (19). Furthermore, ultra structural studies performed by Ostroff *et al.* (20) found that long-term potentiation (LTP) induction in hippocampal slices increased the percentage of spines containing polyribosomes. Strikingly the postsynaptic densities (PSD) in spines containing polyribosomes were larger after LTP stimulation, suggesting that local translation serves to promote the growth of the PSD. Interestingly, another study demonstrated that NMDA-receptor activation promotes the recruitment and sequestration of proteasomes into spines (21). These data suggest that protein translation and degradation within dendrites and spines could effect rapid changes in protein turnover. Thus far it has been difficult to observe protein translation directly in spines. There is, however, ample evidence for specific protein synthesis in synaptosomes (biochemical preparations of detached synaptic spines containing presynaptic terminals) and synaptoneuroosomes (subcellular preparation enriched in presynaptic structures with attached postsynaptic densities). These preparations retain a resting membrane potential and release neurotransmitters when electrically stimulated (22). Using these synaptic preparations, the mRNAs present at the synapses have been described (23,24), and an increase in specific mRNAs after neuronal activation has been demonstrated (25). Furthermore, CaMKII $\alpha$  (26,27), PSD95 (27), Arc (28), and several other proteins are synthesized in these synaptic preparations and their translation is modulated by stimulation. In line with this, a proteomic study in synaptosomes from the

squid optic lobe after metabolic labelling with  $^{35}\text{S}$ -Met, showed de novo synthesis of 80 protein species, including chaperones such as HSP70, mitochondrial and cytoskeletal proteins (29). This study expands the protein families translated in synaptic compartments beyond exclusively synaptic proteins or neuron-specific proteins. Nevertheless, the role of these proteins in synaptic function has not been studied. The development of new techniques improving the isolation of synaptosomes will contribute to a more precise study of their protein content and the newly synthesized proteins in response to different neuronal stimulus (30). Altogether, these findings support the notion that local protein synthesis has a role in synaptic plasticity, but how is this local translation regulated in response to synaptic activity? The localization of mRNAs is thought to play a major role in the regulation of local translation, for example see (31). One important feature of the mRNA is its ability to be spatially localized, this feature derives from untranslated information in the 3' or 5' ends where multiple regulatory elements are located. The transport, localization, stabilization, and translation of the mRNA are often regulated by these elements (32). Recent studies with high resolution *in situ* hybridization data and deep sequencing show that mRNA molecules are distributed in local domains, and more than 2500 mRNAs can be detected in the neuropil (11). In addition to all these regulatory layers associated with the mRNA, there is a regulation in response to activity at the level of translation factors, some of the best known are eEF2 and its kinase eEF2K, (33-35). Phosphorylation of eEF2 is increased in response to NMDAR activation; this inhibits the elongation of most of mRNAs but increases the elongation of some dendritic mRNAs such as Arc or CaMKII $\alpha$  (36,37). Other translation factors with a putative role in synaptic plasticity are eIF2 $\alpha$  (38,39) and 4EBP (40). The regulation of protein synthesis in response to synaptic activity is extensively studied, and is a tightly regulated process able to adjust protein synthesis in response to specific neuronal stimuli.

### 3\_Local Protein degradation

Protein degradation is one crucial component governing protein turnover. The ubiquitin proteasome system (UPS) is an important mechanism for cytosolic protein degradation (41). In HeLa cells the proteins that comprise the proteasome represents 0,6% of the total cellular proteins (42). While the study of protein degradation by the UPS in neurons has gained attention during the last years, the mechanisms underlying proteasome-mediated degradation, local polyubiquitination, and the influence of neuronal activity on local or global protein degradation remains poorly understood. There is, however, increasing evidence for a role of the UPS in neuronal development, neurotransmitter release, synapse vesicle recycling, and learning. The UPS pathway is composed of several enzymes including the proteasome, ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), ubiquitin-ligases enzymes (E3), and deubiquitinases (DUB). All these enzymatic activities give to the pathway a fine-tuned precision for the temporal and spatial regulation of protein degradation. But, is this pathway regulated by synaptic activity and if so, which steps of the pathway are regulated? Indeed, *in vivo* studies have shown that inhibition of the proteasome has consequences for learning. In rats, bilateral infusion of the proteasome inhibitor Lactacystin (administrated 4-7h after training but not after 10h) to the CA1 region of the hippocampus caused full retrograde amnesia for a one-trial inhibitory avoidance training, indicating that the ubiquitin-proteasome cascade is crucial for long term memory (LTM) in the behaving animal (43). Likewise, incubation of rat hippocampal slices with proteasome inhibitors decreased LTP at the Schaeffer collateral-CA1 synapses (44). There is also evidence for a role of deubiquitinating enzymes in learning. One example that, interestingly involves transcription, is Ap-uch (an ortholog of the mammalian deubiquitinase UCH-L1): During long-term facilitation (LTF) in *Aplysia californica* the transcription factor CREB (cAMP-response-element-binding) is activated, stimulating the transcription of Ap-uch, this increases the degradation of protein kinase A regulatory subunits leading to an increase in the catalytic activity of

PKA that is responsible for LTP maintenance (45,46). Similarly, in mice, UCH-L1 inhibitors reduced LTP in hippocampal slices (47). Another example of a DUB enzyme that regulates plasticity, comes from the Usp14<sup>ax-j</sup> mice, defective in the Usp14 deubiquitinase. These mice have defects in hippocampal short-term synaptic plasticity but not in long-term plasticity (48). In addition, E3 enzymes have also been related to plasticity. Hundreds of E3 ligase enzymes have been identified. These enzymes provide specific ubiquitination for particular proteins, representing one of the most complex regulatory steps in the pathway. One example are the APC/C ligases, these multisubunit RING finger E3s ligase comprise 12 different subunits, and some of them target the APC/C to different substrates. The cytosolic APC/C-Cdc20 has a role in dendritic morphogenesis (49) and the nuclear APC/C-Cdh1 regulates axonal growth (50). Furthermore, APC/C-Cdh1 is required for associative fear memory and LTP in the amygdala in mice (51), and for mGluR-dependent LTD in the hippocampus (52). Another example is the E6-AP ligase (Ube3A). Mutations in this protein are associated with deficits in contextual learning (fear conditioning), and with decreased LTP (53). Interestingly, this ligase is associated with the neurological disorder known as Angelman Syndrome (54). E6-AP ligase mediates the polyubiquitination of Arc, and its disruption increases Arc expression and thereby decreases the number of AMPA receptors at synapses (55). In addition, regulation of ubiquitination is sometimes also regulated by other post-transcriptional modifications such as phosphorylation; this is the case of the actin-binding protein SPAR. The degradation of this protein is regulated by an elegant mechanism, which involves activity-dependent induction of a kinase that phosphorylates SPAR promoting its polyubiquitination and subsequent degradation, culminating in the loss of spines (56). Finally, in the last step of the pathway, the proteasome itself, we find another layer of regulation that is also critical for local control of the synaptic proteome. Recent findings show that the proteasome complex is regulated by at least four different mechanisms: by its subunit

composition, its proteolytic activity, its location within the cell, and its interaction with other proteins, all of which are regulated by neuronal activity. These facts were demonstrated by several studies, among them Tai *et al.* found that the treatment of neurons with the glutamate receptor agonist NMDA causes disassembly of the 26S proteasome, decrease in its proteolytic activity and dissociation from the proteasome of the E3 ligases UBE3A and HUWE1, that in non-stimulated conditions co-sediment with proteasomes (57). In contrast, a different study showed that after the blockade of neuronal activity in cultured hippocampal neurons using Tetrodotoxin (TTX, a blocker of the voltage-gated sodium channels) there is a decrease in the degradation rate of the chimeric proteasome substrate GFPu, whereas, an increase in neuronal activity (using Bicuculline, a competitive antagonist of GABA<sub>A</sub> receptors) increases the degradation of GFPu (58). Interestingly, proteasome inhibitors block spine outgrowth in response to glutamate, through a mechanism that involves the phosphorylation of the proteasome by CaMKII $\alpha$  (59). Furthermore, the sequestration of the proteasome in spines is controlled by neuronal activity through CaMKII $\alpha$ , which also regulates its proteolytic activity (21,60). These data suggest a very tight regulation of proteasome degradation in response to the activation/inhibition of specific neurotransmitter receptors that has both early and late components.

Although it is known that a large amount of protein degradation occurs via the action of the proteasome pathway, how degradation itself is regulated by activity remains an interesting question. For example, Ehlers found that treatment of neurons with activity blockers resulted in a decrease of ~50% in the polyubiquitinated proteins in PSD fractions, whereas treatment of neurons with activity inducers results in an increase in polyubiquitinated proteins (61). Nevertheless, only a handful of proteins have been described to change their polyubiquitination status in response to neuronal activity, including scaffold molecules such as Shank, AKAP79\150, GKAP, and PSD95 (61,62). In conclusion, more extensive studies identifying

proteasome substrates in the context of neuronal activity would contribute to a better understanding of the role of proteasome pathway in synaptic plasticity. Something more complex would be the investigation of the regulatory elements of the pathway in a spatiotemporal context. For example, where within the neuron are specific proteins ubiquitinated and degraded? Also a more detailed knowledge of the proteasomal subunit composition and its processing state is desirable. For example does the protein composition of the proteasome and tightly associated proteins change depending on the location within neurons? It is the proteasome more active in specific locations? Is proteasomal activity and subunit composition modulated by synaptic plasticity? In this context, a novel technique that allows for the detection and quantification of conformational states of proteasomes *in situ* using electron cryotomography with a Volta phase plate could be useful (63). Using this technique the authors found that in intact hippocampal neurons only 20% of the 26S proteasomes are engaged in substrate processing, suggesting that the capacity of the proteasome is only partially used in the conditions of this study. This technique could also be used to study structural changes in the proteasome in response to activity (63). In conclusion, and similar to protein synthesis, protein degradation is strongly regulated in neurons.

#### **4\_Coordination of protein synthesis and degradation**

As explained above, it is clear that local protein synthesis and local protein degradation play a role at synapses, implying that crosstalk between these two systems must occur in order to maintain protein concentrations in the appropriate range. Indeed, the co-application of proteasome blockers and translational inhibitors restores L-LTP, which is otherwise blocked when these inhibitors are applied separately. This suggests that a balance between protein synthesis and degradation is needed for L-LTP to occur (64), but the underlying molecular mechanisms are not known. However, it is clear that the UPS is responsible for the

degradation of many proteins that are essential for protein synthesis, and many steps of protein synthesis are controlled by the UPS (65,66). Intriguingly, some of the proteins encoded by the Immediate Early Genes (IEG) with a role in neuronal plasticity, such as Arc (67), or the transcription factor ApC/EBP (68), are degraded by the UPS under specific conditions. Furthermore, Egr1, another IEG protein, regulates the expression of some of the proteasome subunits genes (69). The UPS also has a role in RNA regulation since some RNA binding proteins (RBPs) are degraded through this pathway, these proteins have diverse functions, such as the regulation of mRNA stability, splicing or transport. One example is the RBP FMRP (fragile X mental retardation protein), a regulator of dendritic translation that is degraded by the proteasome (70). Similarly, Mov10 (homolog of the *Drosophila* DExD-box protein Armitage) a component of the RISC (RNA-Induced Silencing Complex), is degraded in response to NMDA treatment by the UPS, and its degradation relieves translational silencing of specific mRNAs such as CaMKII $\alpha$ . As a consequence, after NMDA stimulation there is a 30% reduction in the translation of the CaMKII $\alpha$  in neurons treated with a proteasome inhibitor compared with neurons treated only with NMDA (71). Finally, mRNA stability is also regulated the UPS. There are RBPs that bind to AU-rich-elements (ARE) which control mRNA stability. Interestingly, 5-8% of human genes encode transcripts that contain these elements. One example of an ARE-containing mRNA is the mRNA encoding for ApC\EBP protein, this protein plays a role in synaptic plasticity, and one of the RBPs that regulates ApC\EBP mRNA stability is ApAUF1 (72). Some of the isoforms of mammalian AUF1 are well-established proteasome substrates (73). As such, the UPS is potentially able to regulate the ApC/EBP mRNA and protein. Taken together, these data point to a clear coordination between protein synthesis and protein degradation, but how these two processes are co-regulated by synaptic activity remains to be elucidated.

#### **5\_Protein turnover**

As mentioned above, protein synthesis and

degradation define protein turnover rates. Interestingly, different protein turnover rates have been observed in different tissues (74). For example, one study found slower protein turnover rates in the brain with an average lifetime of 9 days, whereas the average protein lifetime is 3 days in liver and 3,5 days in blood (75). These differences are not only due to stable proteins that are uniquely expressed in the brain, but also to the fact that some ubiquitous proteins have longer half-lives in the brain, by a factor of two to five. This is the case for a number of subunits of the proteasome, for which average half-lives of 8 and 4 days have been measured in brain and liver, respectively (75). Taken together these data suggest a special protein turnover mechanism in the brain, compared with other tissues. Additionally, the studies described in the previous sections suggest that some proteins may display different turnover rates depending on their location in the neuron, and/or depending on the activation state of the neuron. Furthermore, the turnover rate of some proteins may differ among synapses or dendritic branches, as a function of their activation state that can be modulated by their location, posttranscriptional modifications or protein-protein interactions. This idea is supported by some apparent discrepancies in the half-life of the same protein, depending on the cellular fraction studied (see table 1). One nice example is the synaptic protein PSD95 with a reported half-life in total protein extracts of ~88 hours (76), and ~8 hours in synaptic fractions (61). In this context, it is important to note that the techniques used in these studies were different, and the time of protein labeling was also different (7 days vs 12h), this could result in the labeling of different populations of PSD95 with distinct turnover rates [for a review of strategies for turnover analysis see (77)]. Interestingly, another study found a slower GluR1 turnover rate after synapse formation: in mature neuronal cultures (11 DIV) GluR1 has a half-life of ~31h, in contrast, in neurons cultured for 4 days the reported GluR1 half-life is ~12h (78). The occurrence of different turnover rates for the same protein among different cellular compartments has been recently

demonstrated in HeLa cells, comparing the nucleus, nucleolus and cytoplasmic protein turnover rates (79). In this study ribosomal proteins exhibited a fast turnover in the nucleolus (6h) and slower turn over in the cytoplasm (>30h); the authors also found differences in the turnover rates of some proteasomal subunits.

Additionally, the fate of some molecules can also be dependent on their age. For example, in a recent study it was demonstrated that PSD95 proteins less than 6h old are found in immature synapses, while they are less abundant at mature spines where older populations of PSD95 are preferentially found. Therefore, new molecules of PSD95 not only replace the older ones, but also are located at different places, and may have different functions in different areas (80).

Consequently, a systematic comparison of the protein turnover rates in synaptic preparations versus total protein extracts from neurons at different maturity states, could contribute to a better understanding of how this process is regulated in neurons. Furthermore, in recent years, new and exciting alternatives for the measurement of protein turnover *in situ* have been developed. An interesting example is the new microscopy technique denominated COIN (correlated optical and isotopic nanoscopy) (81), which detects newly synthesized proteins labeled with  $^{15}\text{N}$ -Leucine. Using this procedure, protein turnover in several neuronal organelles was measured ( $^{15}\text{N}/^{14}\text{N}$  ratio). Interestingly, the authors focused on the presynaptic compartment and found some synapses with stronger protein turnover compared with the neighboring axon, and clusters of bassoon molecules with different incorporation ratios of  $^{15}\text{N}$ -Leucine, indicating the coexistence in the synaptic area of protein groups with low and high turnover rates (81). A more established technique developed by Schuman and colleagues, FUNCAT (Fluorescent Non-Canonical Amino acid Tagging), consists of the tagging of proteins with non-canonical amino acids and subsequent detection by fluorescent labeling *in situ*. This technique has been successfully applied to primary neurons, organotypic slices, and *in vivo* in larval Zebrafish (82,83). Combining FUNCAT labeling with the proximity ligation assay technique (PLA) (84) it is now

possible to detect *in situ* the synthesis and degradation of specific proteins (85). In a similar way, combining puromycin labeling with PLA the synthesis of specific proteins can be detected within 0,5-1 minute (85,86). Furthermore, photocaged-puromycin that can be locally activated allows for protein synthesis detection in a spatial restricted manner (87). Similarly, the TimeStamp technique allows for the tracking of an exogenously expressed protein fused to drug-controlled tags for detection of proteins synthesized at defined time points; these fusion proteins can be detected by live microscopy or electron microscopy (80). Finally, for studying the modulation of the synaptic protein turnover by mass spectrometry, the use of quantitative noncanonical amino acid tagging (QuaNCAT) is an elegant technique; it combines BONCAT with stable-isotope labeling of amino acids in cell culture (SILAC) constituting a powerful assay to measure protein turnover (76). Collectively, these techniques open new exciting approaches for the study of local protein metabolic turnover in cell lysates and *in situ*.

## 6\_Concluding remarks

Protein synthesis and degradation work together to maintain and regulate synaptic protein turnover; both systems are modulated by different forms of synaptic plasticity. Of special interest is to know how the components of both pathways are distributed in the different neuronal compartments, such as synapses, dendrites, axons or the cell body. A deeper knowledge of this distribution would help us understand the local regulation of protein synthesis and degradation. In addition, it will be important to study if there are compartment-specific characteristics of the synthesis and degradation machinery like specific protein isoforms, specific posttranscriptional modifications, or specific interactors. And, in the case of mRNA, the identification of specific elements regulating the location, its stability and its availability to be translated

is of great interest. Despite an increasing attention in the role of protein synthesis and degradation in neuronal function and plasticity many questions remain open. For example, how are protein synthesis components coordinated for controlling the synthesis of specific sets of proteins required in each location? How and where are protein synthesis and degradation components influenced by post-translational modifications or protein-protein interactions? And how is all this modified by neuronal activity to regulate the synthesis and degradation of specific proteins at specific locations? In addition, how is the destruction of proteins coordinated with the creation of new ones? And how is all this coordinated to achieve synaptic plasticity? A good starting point to answer some of these questions would be to know which proteins are modified in response to the different plasticity paradigms. A detailed study of those proteins and their interactors would help us to understand the spatial and temporal regulation of protein turnover controlled by protein synthesis and degradation and its role in synaptic plasticity.

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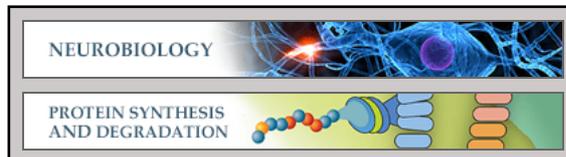
**Table 1:** General protein half-lives in neurons, and specific protein half-lives for endogenous neuronal proteins.

<b>General protein Half-lives</b>				
<b>Total PSD proteins*</b> (61)		Half life~3,28h		
<b>Neuronal proteins (76)</b>		All identified proteins ~121h Synaptic proteins ~99h		
<b>Specific protein Half-lives</b>				
<b>GluR1</b>	Half life~12h <sup>35</sup> S-Met Pulse: 30min DIV: 4 (78)	Half life~31h <sup>35</sup> S-Met Pulse:30min DIV: 11 (78)	Half life~30h <sup>35</sup> S-Met Pulse:1h DIV: 16 (88)	
<b>GluR2</b>	Half life~144h <sup>35</sup> S-Met Pulse: 30min <i>in vivo</i> (89)	Half life~47h SILAC (7 days)(76)	Half life~40h <sup>35</sup> S-Met Pulse:1h DIV: 16 (88)	Half life~173h SILAC <i>in vivo</i> (75)
<b>NR1</b>	Half life~13h <sup>35</sup> S-Met Pulse:12h DIV: 14-30 (Isolated PSDs*) (61)	Half life~38h SILAC Incorporation of heavy amino acids up to 7 days DIV: 14 (76)	Half life~34h (Only membrane bound pool) <sup>35</sup> S-Met Pulse:20min DIV: 8-9 (90)	Half life~2h (Only free pool) <sup>35</sup> S-Met Pulse: 20min DIV: 8-9 (90)
<b>PSD95</b>	Half life~8h <sup>35</sup> S-Met (Isolated PSDs*) (61)	Half life~88h SILAC (7 days) (76)	Half life~36h <sup>35</sup> S-Met Pulse: 1h DIV: 14 -17 (91)	Half life~367h SILAC, <i>in vivo</i> Mice age (t0): 9 weeks Incorporation of heavy amino acids up to 32 days (75)
<b>CaMKIIβ-2</b>	Half life~157h SILAC, <i>in vivo</i> (75)	Half life~91h SILAC (7 days) (76)		
<b>CaMKII-α</b>	Half life~20h <sup>35</sup> S-Met (Isolated PSDs*) (61)	Half life~72h SILAC (7 days)(76)		

\*In this study synaptic half-lives show degradation and protein movement out of synapse.

**Minireview:**  
**The Regulation of Synaptic Protein  
Turnover**

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Schuman  
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