In contrast to protein kinases that participate in long-term potentiation (LTP) induction and memory consolidation, the autonomously active atypical protein kinase C isoform, protein kinase Mζeta (PKMζ), functions in the core molecular mechanism of LTP maintenance and long-term memory storage. Here, using multiple complementary techniques for light and electron microscopic immunolocalization, we present the first detailed characterization of the cellular and subcellular distribution of PKMζ in rat hippocampus and neocortex. We find that PKMζ is widely expressed in forebrain with prominent immunostaining in hippocampal and neocortical grey matter, and weak label in white matter. In hippocampal and cortical pyramidal cells, PKMζ expression is predominantly somatodendritic, and electron microscopy highlights the kinase at postsynaptic densities and in clusters within spines. In addition, nuclear label and striking punctate immunopositive structures in a paranuclear and dendritic distribution are seen by confocal microscopy, occasionally at dendritic bifurcations. PKMζ immunoreactive granules are observed by electron microscopy in cell bodies and dendrites, including endoplasmic reticulum. The widespread distribution of PKMζ in nuclei, nucleoli and endoplasmic reticulum suggests potential roles of this kinase in cell-wide mechanisms involving gene expression, biogenesis of ribosomes and new protein synthesis. The localization of PKMζ within postsynaptic densities and spines suggests sites where the kinase stores information during LTP maintenance and long-term memory.

1. Introduction

The ability of protein kinase Mζeta (PKMζ) to maintain long-term potentiation (LTP) and memory is due to its unique structure as an autonomously active protein kinase C (PKC) isoform [1,2]. Full-length PKC isoforms consist of an N-terminal regulatory domain and a C-terminal catalytic domain. Under basal conditions in the cell, the regulatory domain maintains inhibition of the catalytic domain. Second messengers bind to the regulatory domain and induce a temporary conformational change in the enzyme that releases this autoinhibition. Thus, most PKC isoforms, like many other protein kinases and signalling molecules, participate transiently in signal transduction and in the initial induction of LTP.

Protein kinase Mζeta (PKMζ), by contrast, consists of an independent PKCζ catalytic domain, which, lacking the autoinhibition of the ζ regulatory domain, is autonomously and thus persistently active. PKMζ is generated by an internal promoter within the ζ gene that produces a PKMζ mRNA encoding an independent ζ catalytic domain [3] which is transported to the dendrites of neurons [4]. PKMζ mRNA and protein are expressed almost exclusively in brain, whereas the full-length PKCζ mRNA and protein are not expressed in forebrain, except in the lateral olfactory tract [3,5,6]. Therefore, in hippocampus and neocortex, immunostaining with antisera to ζ will specifically determine the localization of PKMζ.

PKMζ protein persistently increases during LTP, and this increase correlates with the extent and duration of synaptic potentiation during LTP maintenance.
Figure 1. For panels a–i, the animals were perfused through the aorta for 3 min with 4% paraformaldehyde (PFA) in phosphate-buffered saline (PBS), pH 7.4. The brains were removed and postfixed overnight in 4% PFA in PBS, pH 7.4 and transferred to 30% sucrose in PBS until the brains were isosmotic with the solution. The brains were quickly frozen in n-methyl-butane, cooled over dry ice, and kept at −70 °C for cryostat sectioning. For panels j and k, after anaesthesia, brains were postfixed in 10% neutral-buffered formalin overnight and embedded in paraffin, as previously described [6].

Figure 2. The animals were perfused through the aorta for 3 min with 4% PFA in PBS, pH 7.4, and the brains were postfixed overnight in the same buffer at 4 °C.

Figures 3–5; electronic supplementary material, figure S1. For pre- and post-embedding immuno-electron microscopy, the animals were perfused through the aorta for 3 min with 4% PFA with 0.2% glutaraldehyde in PBS pH 7.4. The brains were then transferred to fresh fixative for 24–40 h.

(d) Immunohistochemistry

Unless otherwise stated, all experiments were performed at room temperature.

Figure 1. Immunohistochemistry for PKM<sub>z</sub> by light microscopy. For panels a–i, cryostat sections (40 μm, cryostat at −20 °C) were rinsed three times for 5 min each in 10 mM phosphate buffer (PB), pH 7.4. To inhibit endogenous peroxidase, the sections were incubated for 5 min in antiperoxidase buffer (10% methanol, 3% H<sub>2</sub>O<sub>2</sub>, 80% PB, 7% H<sub>2</sub>O<sub>2</sub>), followed by three washes (5 min each) in PB and two washes in PB−0.3% Triton. The sections were pre-incubated 30 min in blocker (PB−1.5% normal goat serum) and then incubated with primary antibody diluted in blocker (γ catalytic: 1: 100) on a shaker overnight at 4 °C. Sections were washed three times (5 min each) in PB−0.3% Triton, blocked for 30 min, and incubated for 1 h in biotinylated secondary antibody (VECTASTAIN ABC Systems, Vector Laboratories, goat anti-rabbit, 1: 500). Sections were washed three times (5 min) in PB−0.03% Triton, once (5 min) with PB−0.3% Triton, blocked for 30 min and then incubated in the ABC reagent (100 μl of solution A and 100 μl of solution B in PB−0.03% Triton; VECTASTAIN ABC Systems). Sections were washed three times (5 min) in PB−0.3% Triton, rinsed twice (5 min) in 0.05 M Tris (pH 7.6) and incubated for 5 min in diaminobenzidine (DAB) reaction (10 mg DAB in 0.05 M Tris, pH 7.5). Colour was developed by incubating the sections in DAB−1% H<sub>2</sub>O<sub>2</sub>. The reaction was stopped by rinsing slices in 0.05 M Tris (pH 7.5). Sections were washed three times (5 min) in PB and mounted with Permound solution (Fisher Scientific). For controls, sections were incubated in primary ζ-catalytic antiserum (1: 100) pre-incubated with immunizing peptide (100 ng ml<sup>−1</sup>) for 1 h before use (b), or in blocker instead of primary diluted in blocker (i).

For panels j and k, immunohistochemistry on parafin-embedded rat brains was performed as previously described [27]. Paraffin sections (8 μm) were deparaffinized in xylene, rehydrated through graded series of ethanol, submerged in 10 mM citrate buffer (pH 6.0) and microwaved for 5 min. Slides were then rinsed in PBS for 5 min, treated with 99% formic acid for 2 min and rinsed in PBS. Sections were treated with 3% H<sub>2</sub>O<sub>2</sub> for 10 min, rinsed in PBS for 5 min, blocked in 4% normal goat serum for 20 min and incubated in primary antibody (1: 200) in a humidity chamber overnight. The sections were then rinsed in two changes of PBS for 10 min, incubated in blocker for 30 min and then for 1 h in biotinylated secondary antibody (goat anti-rabbit 1: 500, VECTASTAIN ABC Systems). Sections were rinsed in water, counter-stained with Gill’s hematoxylin for 5 min, rinsed twice, dipped in blueing solution 10 times, rinsed again, dehydrated and mounted with Permount solution (Fisher Scientific). For controls, sections were treated as
mentioned above with omission of primary antisera (1 : 200) or with antisera preimmune serum (1 : 200) (data not shown).

Figure 2. Immunohistochemistry for PKMζ by confocal microscopy. Vibratome brain sections (40 μm) were rinsed three times (5 min) in PBS, pH 7.4, transferred to 20% DMSO in PBS until the sections were isopycnic with the solution and subjected to six cycles of freezing (−20 °C) and thawing [28,29] to permeabilize without detergent to mitigate compromise of ultrastructural detail. Sections were then incubated for 10 min with 0.1% glycine in PBS to quench free aldehydes, and rinsed with PBS for 10 min.

The sections were then incubated in blocking buffer (5% normal goat serum in PBS) for 1 h and then overnight in primary antibody (1 : 200) in blocking buffer (a–c), or blocking buffer alone as control (d). The sections were then rinsed in PBS, four times for 20 min each and incubated with goat anti-rabbit Alexa Fluor 488 (1 : 200) in blocking buffer overnight on a rotator
at room temperature in the dark. The sections were rinsed three times in PBS, washed in distilled water and mounted on glass slides with Prolong Gold (Molecular Probes, Eugene, OR, USA).

Figures 3a–d and 4, and electronic supplementary material, figure S3b. Pre-embedding immuno-electron microscopy for PKM$_z$. After fixation, 50 μm vibratome sections were stored in PB with 0.02% sodium azide for up to two weeks. To inhibit endogenous peroxidase, the sections were incubated for 5 min in 3% H$_2$O$_2$ in PB followed by three washes, 5 min each, in PB. Sections were incubated in 0.1% glycine in PB to quench aldehydes for 30 min, rinsed in PB three times, 10 min each, permeabilized with 0.05% Triton X-100 in PB for 30 min and then rinsed as before. Sections were blocked with 5% normal goat serum, 0.1% bovine serum albumin (or 0.1% acetylated bovine serum albumin for electronic supplementary material, figure S3) and 0.1% cold-water fish gelatin in PBS for 1 h, incubated in primary antibody diluted in the blocking solution at 4°C overnight (1 : 200) and then rinsed three times with PB. For DAB, the sections were incubated 2 h with goat anti-rabbit biotinylated secondary antibodies. After rinsing with PB, the sections were incubated in streptavidin–horseradish peroxidase for 1 h, rinsed and developed in DAB solution for 12 min. For pre-embedded immunogold (see electronic supplementary material, figure S3b), after rinsing with PBS containing 0.1% acetylated bovine serum albumin and 0.1% cold-water fish gelatin (washing solution) for 2 h, the sections were incubated overnight with Alexa Fluor 488 FluoroNanogold Fab' fragment of goat anti-rabbit IgG (1.4 nm diameter) secondary antibodies in the washing solution. Sections were then extensively rinsed (12 × for 20 min each) with washing solution and then incubated in PBS overnight. The sections were fixed in 4% PFA and 0.2% glutaraldehyde for 1 h. After fixation, the sections were washed in PBS (2 × 10 min each) and transferred to enhancement conditioning solution (ECS, Aurion, The Netherlands) for four washes, 15 min each. The sections were then silver intensified with silver HQ (Aurion) for 100 min and transferred to ECS containing 50 mM sodium thiosulfate for 15 min.

For both DAB and silver-intensified gold, sections were rinsed in PB and postfixed in 1% OsO$_4$ in PB for 1 h. Sections were then dehydrated in a graded series of ethanol 50, 70, 80 and 95%, followed by three changes of 100% ethanol. Sections were then immersed in a mixture of 1 : 1 ethanol and Embed 812 resin (Electron Microscopy Sciences, Fort Washington, PA, USA) for 1 h, transferred to 100% Embed 812 and then embedded between two Aclar plastic sheets at 60°C overnight. CA1 was dissected from the hippocampus, re-embedded in a BEEM capsule and sectioned at either 1 μm, mounted on a glass slide, and counterstained with 0.5% azure B and methylene blue (figure 4a and electronic supplementary material, figure S1a), or at 80 nm, mounted on grids, stained with 4% uranyl acetate and lead citrate [30] and examined with a Zeiss EM10c transmission electron microscope (Zeiss, Germany) (figures 3a–d and 4b–f). For controls (see electronic supplementary material, figure S1), sections were incubated in blocking solution without primary antibody.
Post-embedding immuno-electron microscopy was performed as previously described by Bergersen et al. [160 et al. [31], with few modifications. After fixation, 50 µm vibratome sections from CA1 region of rat hippocampus were collected. Pyramidal cell layer and radiatum from CA1 were dissected and cryoprotected in 30% sucrose. The samples were then placed into liquid propane and cooled to −190°C with

Figure 3. Postsynaptic distribution of PKMζ in pyramidal neurons of the hippocampus. (a–d) Pre-embedding immuno-electron microscopy for PKMζ detected by DAB staining. PKMζ label is predominantly postsynaptic but varies from striking involvement of the PSD (a–d, small black arrowheads) to absent (a, small white arrowhead). Occasionally, the immunoreactivity extends beyond the PSD to involve the entire spine (b,d, large black arrowheads). By contrast, presynaptic terminals (b,c, large white arrowheads) are immunonegative. (e–h) Post-embedding immuno-electron microscopy for PKMζ detected by immunogold. PKMζ is in spines near or associated with the postsynaptic density (e,h, small black arrowheads). (f) Oblique view of PSD shows abundant PKMζ immunostaining. PKMζ is also observed in clusters within spines (e,g,h, large black arrowheads). Scale bars: (a) 0.55 µm, (b) 0.45 µm, (c,d) 0.53 µm, (e) 0.875 µm, (f) 0.45 µm, (g) 0.68 µm, (h) 0.50 µm.
liquid nitrogen in a Leica CPC plunge freezer (Reichert-Jung, Wien, Austria). Tissue blocks were transferred with precooled forceps to the freeze-substitution unit (Leica AFS), and immersed in a solution of anhydrous methanol and 0.5% uranyl acetate overnight at –90°C. The temperature was raised stepwise in 4°C increments per hour from –90°C to –45°C, at which temperature it was then maintained for subsequent steps. Tissue samples were washed several times with anhydrous methanol to remove residual water and uranyl acetate. Stepwise infiltration in Lowicryl HM20 (Electron Microscopy Sciences, Hatfield, PA, USA) went from Lowicryl/methanol 1 : 2, 1 : 1 and 2 : 1 (1 h each), to pure Lowicryl (overnight). For polymerization, the tissue was placed in a precooled embedding mould. The polymerization was catalysed by UV light at a wavelength of 360 nm for 2 days at –40°C, followed by 1 day at room temperature. Ultrathin sections (80 nm) were cut with a diamond knife on a Leica Ultracut E ultramicrotome and mounted on Formvar-coated nickel grids. Grids with the ultrathin sections were washed on drops of PBS for 10 min at room temperature, etched for 10 s on drops of saturated solution of sodium hydroxide and washed again in PBS. Sections were then washed for 10 min on drops of PBS containing 50 mM glycine and then on drops of 0.1% sodium borohydride/PBS and blocked for 1 h in PBS containing 4% goat serum and 2% bovine serum albumin. The sections were incubated overnight with primary antibodies (dilution 1 : 100) in blocker solution. The

**Figure 4.** Pre-embedding immuno-electron microscopy for PKMζ. Subcellular distribution of PKMζ in pyramidal neurons of the hippocampus. (a) Light microscopic examination of 1 µm thick plastic sections treated with PKMζ antibody reveals striking somatodendritic label (small arrowheads) of CA1 neurons. Some of these cells also display variable label within their nuclei (large arrowhead) similar to that observed in figure 1. (b–f) Corresponding electron microscopic study of 80 nm thin sections further highlights the distribution of PKMζ immunopositivity in distinct subcellular compartments. Neurites: (b) myelinated axons reveal slight PKMζ immunopositivity in some axons (black arrowheads) and the absence of staining in others (white arrowheads). Nuclei: PKMζ immunostaining in the nucleus varies from neuron to neuron, ranging from no reaction product (ce, large white arrowheads), to those with abundant reaction product (ce, black arrowheads) distributed heterogeneously throughout the nucleus and abutting the nucleoli (d). An electron dense granular structure (e, small white arrowhead, and inset) is observed in a paranuclear distribution in some cells. (f) Abundant reaction product is present in irregular granular structures as well as dispersed throughout the dendritic shaft (small black arrowheads). N, nucleus; n, nucleolus; Ax, axons. Scale bars: (a) 40 µm, (b) 1.2 µm, (ce) 16 µm, (d) 1.5 µm, (f) 1.7 µm, (e, inset) 2.0 µm.

**Figure 5.** Post-embedding immuno-electron microscopy for PKMζ. Subcellular distribution of PKMζ in CA1 pyramidal neurons. Immunogold label is noted within nucleolus (n) (a, arrowhead), nucleus (N) (b, arrowhead and inset), and, close to the nuclear membrane adjacent to nuclear pores (c, arrowhead). (d–f) In the cytosol, PKMζ is observed near the endoplasmic reticulum (d, arrowhead) and in the dendritic shaft as a component of granules of various sizes (e,f, arrowheads and f, inset). N, nucleus; n, nucleolus; ER, endoplasmic reticulum. Scale bars: (a) 1 µm, (b) 1.4 µm, (c,f) 0.8 µm, (d) 0.175 µm, (e) 0.4 µm, (b, inset) 0.24 µm, (f, inset) 0.13 µm.
3–5; electronic supplementary material, figure S2). Consistent with its proposed function to maintain potentiation in specific subsets of synapses during long-term memory storage [1,2], variation in the abundance of PKMζ immunoreactivity is observed by electron microscopy within dendritic spines of CA1 neurons (figure 3). The PKMζ immunoreactivity is often localized within and adjacent to the postsynaptic density (PSD; figure 3, small black arrowheads), and in the centre of spines (figure 3, large black arrowheads), with some spines showing heavy (figure 3a, small black arrowhead) and others light or no immunostaining (figure 3a, small white arrowhead). In addition, PKMζ immunoreactivity is observed within granular structures (figures 4e and 5c,f), as well as more diffusely throughout the dendritic shaft (figure 4f). Within the soma, PKMζ immunostaining is observed in a paranuclear distribution adjacent to the nuclear membrane (figure 2c and electronic supplementary material, figure S3). PKMζ was rarely observed in mitochondria and was not observed in Golgi (data not shown). Axonal projections show weak or absent immunostaining (figure 4b), consistent with the sparse label observed in the white matter by light microscopy (figure 1a,b,f).

(c) Nuclear compartmentalization of PKMζ

The expression of PKMζ in the nuclei of neurons is heterogeneous, varying from strong to very weak (figures 1k and 4e,c,a). In some nuclei, PKMζ immunostaining is widely distributed (figure 4c,e); in others, immunoreactivity is most prominent within nucleoli (figures 1k and 5a), surrounding the nucleolus (figure 4d) and in the region of chromatin projections (figure 5b and inset). Immunostaining is also observed near the nuclear envelope and nuclear pores (figure 5c). The presence of PKMζ in nuclei was confirmed by subcellular fractionation (see electronic supplementary material, figure S4).

(d) Granules and punctate structures

PKMζ immunoreactivity is observed within granules or agglomerates of varying size by light and electron microscopy. They are seen in dendrites and cell bodies of pyramidal cells in hippocampus as well as in cortical neurons in a juxtaparanuclear localization. By light microscopy, punctate PKMζ-immunoreactivity is noted in the cell bodies of some pyramidal cell neurons in neocortex and CA1, mainly in a paranuclear distribution, as well as within dendrites (figures 1k and 2c and electronic supplementary material, figure S2). Dot-like structures are also prominent at some dendritic bifurcations (figure 2c). The number of these paranuclear and dendritic structures varies from animal to animal (data not shown). Pre-embedding immuno-electron microscopy reveals immunopositive granules within cell bodies in a paranuclear distribution (figure 4e and inset), although these are less commonly seen than those observed by light microscopy. Smaller immunopositive granules are commonly noted within dendritic shafts by electron microscopy (figures 4f and 5c,f and inset).

4. Discussion

Here, we present the first detailed investigation at the light and electron microscopic level of the distribution of PKMζ in brain. PKMζ is abundantly expressed in neocortex and hippocampus, consistent with previous quantitative immunoblot [6] and...
mRNA in situ hybridization [4,5]. PKM\textsubscript{z} immunoreactivity is prominent in dendritic spines as well as in nuclei and other intra-neuronal structures associated with gene expression. The varied abundance of PKM\textsubscript{z} among these structures suggests that PKM\textsubscript{z} participates dynamically in multiple cellular processes in the maintenance of synaptic plasticity and memory.

(a) Postsynaptic localization
The localization of PKM\textsubscript{z} immunoreactivity within dendrites, dendritic spines and synapses indicates sites of PKM\textsubscript{z}’s physiological role in the maintenance of LTP and long-term memory [2]. Some synapses are heavily immunostained, whereas others appear not stained at all. This result supports the notion that long-term information is stored as the patterns of synaptic weights, with some synapses maintained in a baseline state by homeostatic processes and others maintained in a potentiated state by LTP [2]. Within spines containing the kinase, PKM\textsubscript{z} is found in multiple locations—within the PSD, adjacent to the PSD and in clusters at the centre of the spine. This variation in intraspine location is consistent with PKM\textsubscript{z}’s proposed mechanism of synaptic potentiation by altering the dynamics of AMPA receptor trafficking into and out of the PSD through the regulation of receptor endocytosis [2,32]. Initial work with mouse knock-outs of PKM\textsubscript{z} have questioned the role of PKM\textsubscript{z} in synaptic plasticity and memory [33,34], reporting normal LTP and long-term memory in the constitutive PKM\textsubscript{z} knock-out for various tasks. More recent studies, however, have found compensation in the constitutive knock-out by other PKC isoforms [35], particularly with the other atypical isozyme, PKC\textsubscript{i}, that mediates early-LTP expression [36]. Blocking PKM\textsubscript{z} gene expression by either antisense oligodeoxynucleotides in wild-type rats and mice or conditional knock-out in mice prevents late-LTP and long-term memory [37]. The postsynaptic localization of PKM\textsubscript{z} in normal animals observed in the current study further supports the function of PKM\textsubscript{z} as an active mediator of synaptic strength. Quantification of the subcellular distribution of PKM\textsubscript{z} in spines after LTP and memory formation will be an important area for future investigation.

Our current results are consistent with the recent quantitative electron microscopic analysis in dentate gyrus of rhesus monkeys by Hara and co-workers [38], who used an antibody recognizing atypical PKC (both \(\zeta\) and \(\lambda\) isoforms), as well as a second antibody recognizing AMPA receptor subunit GluA2, whose postsynaptic trafficking is regulated by PKM\textsubscript{z} [32,39,40]. They found that higher proportions of dendritic spines coexpressing these two molecules correlated with faster delayed non-matching-to-sample-task acquisition and more accurate recognition memory [38]. Their findings are compatible with the synaptic localization of PKM\textsubscript{z} demonstrated here and PKM\textsubscript{z}’s role in GluA2-mediated AMPA receptor trafficking [32,39,40].

(b) Nuclei and nucleoli
The variability observed in nuclear label, from intense to undetectable, suggests that PKM\textsubscript{z}’s function in the nucleus may also be dynamically regulated, perhaps as a consequence of long-term changes in the capacity of specific networks of neurons to sustain plastic changes. In particular, the localization of PKM\textsubscript{z} to chromatin raises the possibility that the kinase may be important for epigenetic regulation of gene expression, a process well known to regulate synaptic plasticity [41,42], initial memory consolidation [43,44], as well as memory maintenance [45]. Within nuclei, PKC\textsubscript{z} has been reported to phosphorylate nucleolin, an important regulator of chromatin remodelling and gene expression [46,47]. Our finding that PKM\textsubscript{z} also localizes to nucleoli (figure 5a), suggests the possibility of a role in ribosomal RNA synthesis and the processing and the biogenesis of ribosomes.

(c) Dendritic punctate structures
PKM\textsubscript{z} immunoreactivity was seen within granules or punctate structures of varying size in dendrites and the cell body. Similar structures, observed by others in neurons have been referred to as botryosomes [48], or other terms [49], which have been described as nucleoli-like structures located in the cytoplasm that have no membrane boundaries. The function of botryosomes is not clearly established, but they may play a role in protein synthesis [50]. Botryosomes have been shown to increase with neuronal plasticity [48,51,52] and neurite outgrowth [53] and have been reported to contain AMPA receptors [54].

(d) Localization to multiple sites of gene expression and the role of PKM\textsubscript{z} in plasticity-regulated synthesis of PKM\textsubscript{z}
PKM\textsubscript{z} has been proposed to regulate its own synthesis in both the induction and maintenance of LTP and long-term memory. PKM\textsubscript{z} has been shown to regulate new protein synthesis during the induction of LTP, including, in a positive feedback loop, its own translation from PKM\textsubscript{z} mRNA [11,12]. In addition, because PKM\textsubscript{z} maintains neocortex-dependent memories for up to three months, if the half-life of the kinase is shorter than the duration of PKM\textsubscript{z}-dependent memory, then increased synthesis of PKM\textsubscript{z} might be continually required to perpetuate these very long-term memories. Thus, the distribution of PKM\textsubscript{z} in the cell-wide, gene expression machinery may be part of an extensive positive feedback loop to maintain increased amounts of the kinase that could be available locally to synapses at levels appropriate for synaptic potentiation [2].

In conclusion, PKM\textsubscript{z} is widely expressed in pyramidal neurons with intracellular compartmentalization in structures that mediate both gene expression and excitatory synaptic transmission. PKM\textsubscript{z} functions in synaptic plasticity to regulate activity-dependent, new protein synthesis [11], and metaplastic [13,21,22] and neuroprotective [23] roles of PKM\textsubscript{z} have also been reported. Although localization to a specific intracellular compartment does not indicate function within the structure, the presence of PKM\textsubscript{z} in nucleus, nucleolus, botryosome-like structures and endoplasmic reticulum suggests the possibilities that PKM\textsubscript{z} functions in gene expression, biogenesis of ribosomes and new protein synthesis. The variation in abundance of PKM\textsubscript{z} at PSDs and spines supports the cognitive role of PKM\textsubscript{z} in storing information at synapses by the molecular mechanism of LTP maintenance [2].

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