The molecular memory switch

PKMζ and its role in maintaining old memories

- Memory is crucial for everyday life and memory dysfunction underlies serious conditions such as post-traumatic stress disorder (PTSD), Alzheimer's Disease (AD) and neuropathic pain.
- Synaptic long-term potentiation (LTP) is thought to be the cellular basis of memory. How LTP is maintained over years, however, is still unknown.
- At BioSystOmics, USA, research by Dr Naveed Aslam highlights the protein PKMζ as a molecular switch key to long-term memory, which creates a positive feedback loop capable of maintaining LTP at a synapse over years in a self-sustaining manner.
- Targeting PKMζ activity may enable new treatments for memory-related disorders.

It's a familiar and shared experience – you're drifting off to sleep at night, and suddenly your brain decides to relive that painful memory you'd rather forget. Wouldn't it be great if we could just delete these excruciating memories, like deleting a file from a computer? How about if you could boost specific memories, so you never forget that important anniversary, you ace that exam you've been studying for, or just so you don't forget where you put the keys again? New research from Dr Naveed Aslam, Director of Research & Development at BioSystOmics, USA, offers an exciting glimpse into a future where we can manipulate biological memory, as well as highlighting some potential targets for therapeutic intervention.

I remember, therefore I am

Memory is vitally important, not just for everyday life: your collection of stories and experiences is what makes you, you. Of course, beyond the embarrassing memories and trivial forgetfulness, there are more serious conditions relating to memory dysfunction, such as neuropathic pain, phantom limb syndrome, post-traumatic stress disorder (PTSD), neurodegeneration, and dementia. Treating these disorders will require a detailed knowledge of the biological basis of memory – an area of active research. Much progress has been made in this field, which has led to our current understanding of neuronal synaptic plasticity and a mechanism called 'long-term potentiation' (LTP), thought to be the cellular basis of memory in the brain.

Synaptic plasticity refers to the observation that individual synapses, the contacts between neurons, show use-dependent changes in the efficiency or strength of their synaptic transmission – synapses that receive a lot of input tend to become stronger, and those that don't are diminished and often eventually removed entirely. LTP is the mechanism by which this is achieved. Put simply, LTP results in stronger synaptic transmission and is induced by frequent activation of the synapse. However, a key unresolved question is how LTP, and therefore specific memories, can be maintained over the course of years, when the lifetime of most of the key proteins found at the synapse is in the order of hours. This is where Dr Aslam's research comes in, building on prior work identifying a brain-specific protein kinase that is now considered one of the key candidates for long-term memory maintenance, called PKMζ.

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PKM zeta – the molecular memory machine

As Dr Aslam explains, 'PKMζ is considered as an engine for memory storage. By inhibiting this molecule memories can be erased without damaging the brain or permanently disrupting memory function.' Previous research has shown that PKMζ is formed during the initiation of LTP, and once active, maintains synaptic potentiation by trafficking key synaptic transmission receptors, called AMPARs, into the post-synaptic membrane, thereby enhancing signal reception. This does not explain how this potentiation is maintained over the course of months or years, however. Dr Aslam's new research addresses this question directly – he describes a mathematical model showing how PKMζ could act as a bistable molecular switch, resulting in a positive feedback loop independent of external stimulus. By driving its own activation and production through local translation at the synapse, the activity of the protein, and therefore LTP, can be maintained at an individual synapse much longer than the lifespan of an individual PKMζ molecule.

A molecular switch

The model is based on a molecular network composed of protein translation/degradation and activation/deactivation sub-networks. PKMζ can exist in three activity states, based on phosphorylation status. If unphosphorylated, PKMζ has a very short lifespan. Phosphorylation of PKMζ, which happens during the initiation of LTP, activates the protein and increases its stability, extending its lifespan. If double-phosphorylated, by autophosphorylation, PKMζ has a significantly longer lifetime, and additionally regulates the synthesis of new PKMζ through a local translation feedback loop. It is this regulation of its own activity and local production that results in a molecular 'on/off' switch at the level of an individual synapse, enabling the long-term maintenance of LTP, and therefore long-term memory.

This model is supported by experimental evidence from prior studies. It has been shown that LTP induction leads to an increase in the concentration of total PKMζ in hippocoampal neuron synapses, and that persistent PKMζ activity is necessary to maintain LTP in these cells. It has also been shown that components of the protein translation machinery are constitutively localised at individual synapses, reinforcing the idea of local production of PKMζ. Further support is provided by observations that a PKMζ activity inhibitor, zeta inhibitory peptide (ZIP), rapidly reverses established LTP, and can also abolish spatial memories in rats. Interestingly, ZIP has no effect on the protein synthesis-independent

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phase of early LTP, which is consistent with Dr Aslam's model, where LTP initiation is dependent on the external synaptic transmission signal but requires local production of new PKMζ proteins only for LTP maintenance.

Manipulating memory

The applicability of this research to potential clinical applications is clear. The model predicts that manipulation of the activity or level of PKMζ at the synapse will influence the strength of the memory associated with that neuronal circuit. Neuropathic pain could be treated by reducing the strength of the neural circuits involved in signalling that pain by inhibiting PKMζ. Traumatic memories at the base of PTSD symptoms could be reduced or even removed with accurate targeting of the relevant neurones. Potentially even some of the memory loss associated with dementia could be mitigated by enhancing PKMζ activity or levels.

PKMζ could act as a bistable molecular switch, resulting in a positive feedback loop independent of external stimulus.

However, actually translating this research to viable therapies may take some time. Much work will need to be done on identifying specific target networks, and also delivering any active therapeutic precisely to the network/neurones targeted. Off-target effects of reducing or enhancing general PKMζ levels or activity could be disastrous. With further work to verify the proposed PKMζ regulated model of LTP maintenance, alongside advances in our ability to identify dysfunctional neural circuits and deliver therapies precisely, we may soon be able to manipulate biological memory to a level never thought possible.

Personal response

What are the key unresolved questions that should be addressed by future research in this area?

Following these three questions could make it more interesting:

1. Inhibiting PKMζ has not only been implicated in the erasure of long-term unpleasant or painful memories but it is also linked to strengthening of memories such as in Alzheimer's disease (AD) where memories are falling apart. So, a key question is: What could be the mechanism whereby augmenting new PKMζ is leading to stabilising or strengthening of fading memories? Can the bistable model proposed here still hold or is this a multistate problem? I have developed a mechanistic framework of AD involving key molecular players and I am also planning to link how incorporating PKMζ into this signalling module could explain some of observations in AD patients.
2. Post-synaptic neuronal spine has a small volume so it would be interesting to see how the bistability holds in the stochastic domain of biochemical reactions supporting PKMζ activity. This is even more interesting as we see the phosphorylated and unphosphorylated states are very close to each other in the deterministic model.
3. Also what other key signalling molecules may also play a role in strengthening the feedback loop for on-going synthesis of new PKMζ during the enduring phase of memories. Identifying and incorporating these into base model will certainly add value. I have done some interesting work involving more detailed interactions of PDK1.

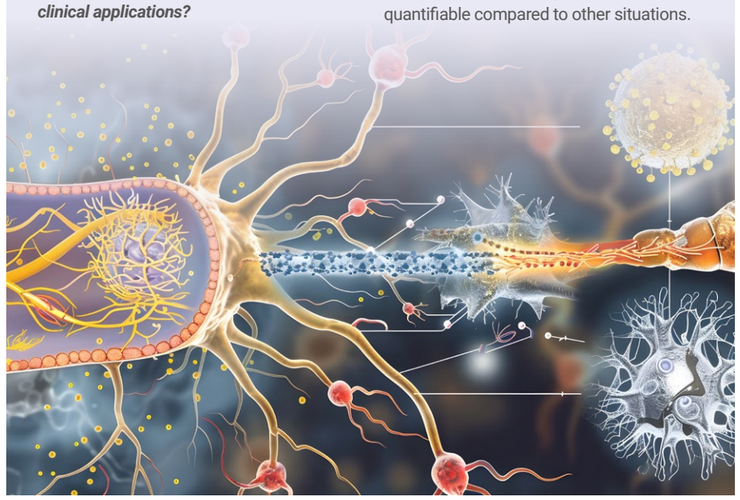
How could this research be translated to clinical applications?

In clinical translation there could be two key focus areas:

1. Erasure of unpleasant or painful memories: Fortunately, we have 'ZIP', which is a specific PKMζ inhibitor, so the next issue is how we get this delivered precisely to the right synapses where PKMζ is active. Devising targeted delivery systems or formulations would be key for clinical translation.
2. Another aspect is the more PKMζ you can provide, the easier it is to stabilise your old memories or better process your lasting memories. This may have to do with making more of new PKMζ particularly at synaptic connections where old memories were originally sitting in the form of active PKMζ. Here, probably a new molecular entity which could strengthen the feedback loop and stimulate the formation of new protein in a synapse specific manner could be critical.

What might be the risks associated with developing these targets for clinical application?

The main concern is the influence of PKMζ on the baseline firing patterns of the mammalian brain and possible associated toxicity with inhibiting or augmenting this molecular memory engine. In the mice model it has been shown that the baseline is unaffected when PKMζ inhibitor is used. However, this needs to be further investigated in diverse human populations under various dosing regimens and settings. So the fundamental concern is how interfering with PKMζ would alter the functionality of the human brain or, for that matter, behaviours and what could be the time scales or genetic compositions where these effects are more pronounced and quantifiable compared to other situations.



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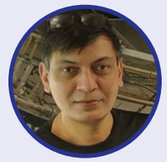

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Bio

Dr Naveed Aslam is Director of Research and Development (R&D) at BioSystOmics. He has 20 years of industrial and academic experience covering R&D, engineering, energy, and translational research. Dr Aslam has 17 published journal papers, with 11 journal papers in review, and 79 conference presentations. He was awarded the Outstanding Research Award, University of South Florida, and Outstanding Research Award University of Texas, Health Sciences Centre Houston, Texas.

Further reading

1. Aslam, N, (2023) Maintenance of PKMζ-modulated synaptic efficacies despite protein turnover. *Front Syst Biol* 2, 933938.
2. Osten, P, et al (1996) Protein synthesis dependent formation of protein kinase M zeta in long-term potentiation. *J Neurosci*, 16, 2444–2451.
3. Serrano, P, et al (2008) PKM zeta maintains spatial, instrumental, and classically conditioned long-term memories. *PLoS Biol*, 6(12), 2698–2706.
4. Yao, Y, et al (2008) PKM zeta maintains late long-term potentiation by N-ethylmaleimide-sensitive factor/GluR2- dependent trafficking of postsynaptic AMPA receptors. *J Neurosci*, 28(31), 7820–7827.
5. Ostroff, LE, et al (2002) Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices. *Neuron*, 35, 535–545.
6. Kelly, MT, et al (2007) Regulation of protein kinase M zeta synthesis by multiple kinases in long-term potentiation. *J Neurosci*, 27(31), 3439–3444.
7. Pastalkova, E, et al (2006) Storage of spatial information by the maintenance mechanism of LTP. *Science*, 313(5790), 1141–1144.