

## **Evidence for long-term potentiation in phospholipid**

**membranes.** Scott HL, Bolmatov D, Podar PT, Liu Z, Kinnun JJ, Doughty B, Lydic R, Sacci RL, Collier CP, Katsaras J (2022 December 13<sup>th</sup>) Proc Natl Acad Sci U S A. 119(50):e2212195119. [PubMed](#)

### Re-interpretation based on the IPL mechanism

Long-term potentiation (LTP) is an electrophysiological finding observed in large number of brain regions where different inputs converge. Large number of correlations were found between LTP and the ability of animals to store associatively learned information and retrieve their memories. However, it is necessary to verify whether LTP can generate cellular changes similar to that occur in physiological conditions *in vivo*.

It was shown that the least path required to induce LTP is the stimulation of postsynaptic terminals (dendritic spines) (Kullmann et al. 1992). Later, it was shown that inhibitors that block postsynaptic membrane fusion attenuate LTP (Lledo et al., 1998) even though it is not clear where exactly this fusion takes place. Using a derived mechanism for generating first-person inner sensations (that provides testable predictions), it was possible to explain LTP in terms of inter-neuronal inter-spine membrane interactions that were called inter-postsynaptic functional LINKs (IPLs). Structure of IPLs varies depending on the inter-membrane interaction that can range between exclusion of hydration layer between membranes and membrane hemifusion (Vadakkan, 2019a). The delay for induction of LTP was explained in terms of time taken for the dendritic spines in a field (containing large number of synapses at a location between stimulating and recording electrodes) to expand and start interacting (Vadakkan, 2019a) (video). Testable predictions for the operational mechanism of IPLs were provided (Vadakkan, 2019b).

Before undertaking any *in vivo* experiments, it is necessary to obtain evidence to suggest whether inter-spine membrane interactions can cause a long-lasting electrical connection between them. Semblance hypothesis proposed displacement of hydration water, from the extracellular space between spine membranes of different neurons at the location of their convergence, that can progress up to the formation of hemifusion between those spine membranes. Semblance hypothesis also

proposed that the area of membrane interaction can act as a passive conductive location between spines that belong to different neurons. Furthermore, this interaction enables input signals arriving from one of the associatively learned stimuli to depolarize the interacting second membrane to generate inner sensation of the second stimulus due to certain specific features at the synapses (explained in Vadakkan, 2013).

A new evidence suggests that inter-membrane interactions between lipid monolayers can lead to membrane hemifusion and generate capacitance at those locations where energy can be stored (Scott et al., 2022). Slow discharge from this capacitor enables these hemifused locations to produce a long-lasting potentiated effect similar to that of LTP. The ability to store charge and its discharge is subsequently match with a property having time-scales suitable to explain working memory. But storing and releasing charge can only explain the electrical findings. More questions remain. "Can such a property be explained between vesicles whose membranes are lipid bilayers?", "How does such inter-membrane interaction contribute to inner sensation of memories?" Semblance hypothesis has provided an explanation of how semblances can be induced at the second inter-LINKed spine as a system property when one of the associatively learned stimuli arrive at the first inter-LINKed spine (Vadakkan, 2013, 2019).

The findings in Scott et al's work show that inter-membrane interaction has the ability to retain hemifused area for certain length of time. If such changes can occur in biological system, it will enable the neuronal cells to take steps to stabilize those interactive areas for a long period. If two associated stimuli continue to arrive frequently, then it is better for the neuronal cells to stabilize the inter-neuronal inter-spine interactive region, if it provides certain cellular level benefits. While this is the primary aim as far as the cells are concerned, it leaves the system with a functional advantage to generate semblances for inner sensations that will enable the animal to survive, which can be viewed as an evolutionarily gained feature.

Scott et al's work provides an explanation that the hemifusion between lipid monolayers can remain stable for certain period without causing mixing of the vesicle contents. It also indicates the possibility that

hemifusion between double membranes can be undertaken in future studies to examine for such possibilities. How does capacitance development found by Scott et al at the locations of hemifusion influence the hemifused areas between lipid bilayers of spines that belong to different neurons? Due to the reason that mean inter-spine distance is more than mean spine head diameter (Konur et al., 2003), inter-neuronal inter-spine interaction leading to IPL formation has been viewed as a candidate mechanism.

Biological systems have several trans-membrane proteins whose extracellular domains can interact in such a way to exclude hydration layer between membranes to promote inter-membrane interactions. For example, SNARE (soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor) proteins are known to provide energy for bringing together membranes against repulsive charges and overcome energy barrier related to curvature deformations during hemifusion between abutted membranes (Martens and McMahon, 2008; Oelkers et al., 2016). They also generate force to pull together abutted membranes as tightly as possible (Hernandez et al., 2012). By initiating the fusion process by supplying energy (Jahn and Scheller, 2006), SNARE proteins can lead to the formation of characteristic hemifusion intermediates (Lu et al., 2005; Liu et al., 2008). These properties of SNARE proteins highlight their functional significance to form hemifusion intermediates that can possibly contribute to IPL formation. These intracellular factors can contribute to a short-lasting inter-spine membrane interaction leading to the generation of a short-lived IPL.

There are several avenues for futures studies in lipid chemistry to understand inter-membrane interactions at locations in the nervous system where extracellular matrix space is very minimal. Manipulating membrane fusion stages using SNARE modulators (Khvotchev and Soloviev, 2022) to understand its effects on LTP, associative learning and memory can lead to further advancements in this area of research.

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