Chromatin plasticity predetermines neuronal eligibility for memory trace formation. Santoni G, Astori S, Leleu M, Glauser L, Zamora SA, Schioppa M, Tarulli I, Sandi C, Gräff J. Science. 2024 Jul 26. Article

Re-interpretation based on the IPL mechanism

Santoni et al. found that neurons in which histone acetyl transferase (HAT) was overexpressed (& that led to increased histone acetylation) are neurons in the engram. Histones are proteins covering DNA. HAT is non-specific regarding the locations from where it removes histones over the DNA sequences that constitute the genes. Histone acetylation by HAT decreases the affinity of histones to DNA, exposing all the genes, which will facilitate transcription. However, in a state of homeostasis where certain specific genes need to be expressed, HAT overexpression is expected remove histones over those genes. Hence, in the case of fear conditioned learning, HAT is expected to promote expression of genes that are essential for learning changes necessary for memory storage.

Using the findings in this paper, it is possible to ask, “Is it providing any interconnected explanation for the semblance hypothesis?” Since IPLs are expected to be formed during learning between abutted spines (of different neurons or different branches of a single neuron), to retain the IPLs for maintaining memory of a survival requiring action, the neuronal cell will restrict using membrane segments from those spines for endocytosis. This can be expected to result as an evolutionary adaptation. Hence, more phospholipid molecules are expected to be synthesized to make lipid membrane segments to retain the formed IPLs. This leads to homeostatic mechanisms to synthesize phospholipids by fatty acid synthesis (mainly palmitic acid) by a multi-enzyme complex consists of seven different enzymes followed by desaturase and elongase enzyme actions, synthesis of phospholipids, their transport and incorporation into the plasma membranes. In these contexts, HAT is expected to remove histones from the corresponding DNA sequences to facilitate expression of a specific set of enzymes.

In summary, HAT injected mice exhibited stronger fear memory because those IPLs that were formed during fear learning, were maintained. It is reasonable to expect that this became possible since there was no homeostatic pressure for their reversal since enzymes along the path of making phospholipid membranes were expressed in sufficient quantity by HAT.

Authors found increased expression of synaptic proteins. Since IPLs are formed between spines that are part of synapses, naturally it will lead to several homeostatic mechanisms to replenish substrates to maintain existing synapses whose spines formed specific IPLs

Optogenetic silencing of the epigenetically altered neurons prevented fear memory recall. Since we are examining behavior, silencing these neurons will prevent their firing, which will not allow firing of downstream neurons to manifest behavioral motor actions (foot withdrawal) during fear memory retrieval.

Note: It is highly necessary to start experiments by making different presuppositions. For example, the present work viewed that memories are encoded by sparse populations of neurons. To understand how memories are stored, it is necessary to view memories as a first-person property and derive a testable mechanism (e.g. the semblance hypothesis) using constraints from a large number of findings in different experiments and test whether derived solution still hold true.