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Review Article

The Transfer of Memory from Short Term Memory to Long Term Memory

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SUMMARY
The mechanism of transfer of memory from short term to long term memory is a subject that has created an interesting avenue for much debates and continuous experimentation. This review discusses the results of such experiments involving hippocampal lesions and pharmacological inhibition. The limitation of these earlier experiments in understanding memory transfer being temporal and cellular precision. Recently, fast optogenetic tools have been used to investigate the role of CA1 neurons of the hippocampus and the anterior cingulate cortex (ACC). The results of these experiments show the contribution of excitatory CornuAmmonis (Ca1) neurons to remote memory recall. It also reveals the plasticity of the mechanisms involved in recall by implicating CA1 in the recruitment of ACC for remote memory recall.

INTRODUCTION

One of the challenging questions in Cognitive Neuroscience is how Short-term Memory is converted to Long-term Memory. The question may be simple in the context of numerous literature on mechanisms of memory storage, however it is a subject of that has created an avenue for much discussion, debate and experimentation. Earlier, the hippocampus was shown the be necessary for retaining context-dependent memories until they are consolidated in their original form in the neocortex.[1,2] Thus, the hippocampus is thought to serve a temporary function in the storage of memory, because, when the hippocampus is damaged, recent but not remote memories are impaired.[3]

An alternative view is that the original memory is transformed from one that is detailed and context-dependent to one that is schematic and generic, capturing the gist of the original.[4] The transformed memory is then represented in areas connected to the hippocampus. When hippocampal lesions are made within short delays and before consolidation has occurred, these interfere with memory.[5,6] However, at long delays, hippocampal lesions had no effect on memory.[5,6] Furthermore, animals retained context-shock association when a long delay was imposed between the time of conditioning and the time of surgery; this supports the notion that the hippocampus has a transient function in the storage of memory [7]. On this basis, it was established that the hippocampus has a temporarily-restricted role in memory storage that is assumed by other structures over time.[5]

Hippocampal Lesion Studies

Using food preference and contextual fear conditioning paradigms, Winocur *et al*. [4] reported results of experiments involving lesions which typically destroyed about 67% of the hippocampus. For contextual fear conditioning, lesioned rats performed poorly in comparison with intact rats at both delays (short or long), which confirms that the hippocampus is crucial for contextual fear conditioning. In the food preference task, there was no difference between lesioned and control rats following one day delay in the same context. At, longer delays, hippocampal lesions caused rats to forget the food preference more quickly. There were notable effects in changing the context at both short and long delays in fear conditioning and food preference tasks. At short delays memory was reinstated in the same, but not the different context in both tasks, whereas at long delays normal rats performed well regardless of context.[4] In contrast, hippocampal-lesioned animals showed diminished memory function even at long delays for the food preference test. This clearly shows that the hippocampus is necessary for retrieving memories at long delays, a shift from an earlier perspective. Although, it was earlier established that recent memories are more vulnerable to hippocampal damage than older memories which are in a more stable form in the cortex, some memory function tests show a different trend.[8] This implies that hippocampal lesions may also affect remote memory recall, and that this method of studying remote memory recall is deficient even when only a specific area of the hippocampus is lesioned.[8]

Pharmacological Inhibition

The first step of memory formation involves creating the potential to form a lasting memory, but not in all cases the commitment to do so.[9] In order to encode episodic memory, the information that an individual receives causes immediate changes in synaptic strength in the hippocampus that constitute one of the initial traces of the experience. A filtering

process associated with synaptic plasticity then ensures that only a subset of these changes are retained to cause lasting traces and so become consolidated.[10] The discrimination or filtering process is now thought to involve an interaction between a local and automatic post-translational tagging mechanism at synapses and a more diffuse up-regulation of plasticity-related proteins.[11]

There appears to be a time-dependent relationship between retention of memory in the hippocampus and in the cortex[4,5,13,14]. Frakland *et al*. [12] reported using Calmodulin-Dependent Protein Kinase II (CaMKII) deficient mice to study the role of the anterior cingulate gyrus participation in remote memory recall and reported that the ACC-activated with the expression of Zinc Finger Transcription Factor (Zif268) in wild type mice tested for remote memory recall but not in mutant CaMKII-deficient mice, showing that the CaMKII is necessary for the elaboration of remote memory in the ACC.[12] Despite the progress with cellular precision, temporal precision was still unresolved.

Optogenetic Inhibition

Taking a step further by applying optogenetics with microbial opsin genes, a method which enables both cell-type precision and temporal control on the millisecond timescale, investigations were conducted capitalizing on the circuit specific for this behaviour with separation between different stages of memory. Optogenetic inhibition was carried out by stereotactic delivery of the Calmodulin-Dependent Protein Kinase II:Natrosomonas Halorhodopsin (CaMKIIα cells: eNpHR3.1) vector which resulted in CA1-specific expression. By applying continuous 561 nm illumination on excitatory CA1 neuron, there was inhibition of spiking in-vivo in a temporally precise, stable, and reversible manner.[15]

Using optogenetic inhibition, contextual fear acquisition and recall of fear memory was blocked in dorsal CornuAmmonis (CA1) neurons. Even though the fear memory was found to be present in a previous test using another method, optogenetic inhibition on CA1 blocked memory retrieval.[15] This suggests a real time involvement of CA1 excitatory neurons in acquisition and recall of recent contextual fear memory without any exploratory or anxiolytic effect found between eNpHR3.1 mice and control mice. Pharmacological inhibition of the hippocampus using TTX (tetrodotoxin) and CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), disturbed recent memory but not remote fear recall with the possible interpretation being that the speed of optogenetic inhibition permits testing without allowing the expression of compensatory mechanisms.[15] The findings support the prior work that the remote memory trace is not stored only by the CA1 hippocampal neurons but that when given enough time to compensate for hippocampal inactivation, the memory can still be retrieved, presumably by other structures. The findings also reveal that the intact hippocampus may be a default activator of the remote memory trace and actively participates in its maintenance throughout the session of recall.[15]

In previous studies, the anterior cingulate cortex (ACC) had been implicated in remote fear memory storage.[12,16] Optogenetic inhibition of ACC either one day or one month following contextual fear had no effect on recent memory but impaired remote memory.[15] Earlier studies reported no detectable increase in hippocampal activity following remote fear recall.[12,16] A decrease in hippocampal activity in the transition from recent to remote memory was also previously observed for recall of a hippocampus-dependent spatial task.[16] This coding may also involve other associated structures in the cortex (for example the ACC) such that a slight increase in activity levels is sufficient for the activation of the memory trace. In simple terms, for remote memory recall, the hippocampus employs the ACC but not for recent memory which is solely dependent on the hippocampus.[15]

DISCUSSION

Cellular precision is crucial in studying the involvement of the hippocampus in remote memory recall, based on the finding that the precise real-time inhibition of the CA1 region, sparing other hippocampal regions such as the dorsal (Dentate Gyrus) DG, and CA3 and ventral CA1, is sufficient to impair remote recall.[15] Temporal precision is supported with evidences that when time to compensate for the absence of hippocampal output is allowed, remote memory recall is no longer impaired.[15] Brain imaging results showed increase in ACC activity with remote call.[15-17] In addition, CA1 inhibition during remote recall reduced the neuronal activity in ACC. The finding that both CA1 and ACC inhibition interfere with remote recall could also support the “Transformation Theory”.[18] This suggests that in system-wide consolidation, the memory is not merely copied from hippocampus to cortex but rather transformed, and that both memories remain available, with continuous interplay.[4] At this point, it is imperative to investigate the mechanisms by which the hippocampus serves as an information transfer unit conveying some aspects of perception of the context to the ACC. Based on the research findings discussed in this review, memory can be termed 'a dynamic physiological process' involving hippocampal and cortical interaction which is still being unravelled.

CONCLUSION

Previously it was believed that memory was transferred from the hippocampus to the cortex as long-term memory such that during memory recall, the hippocampus is not involved. However, we now know that the hippocampus is involved during memory recall showing the dynamics of memory function in the brain. In pursuing a deeper understanding of the dynamics of memory function in the brain, the fast optogenetic inhibition has shown to be a valuable tool for further investigations based on the remarkable results it has provided so far. Together with brain mapping techniques, it is believed that Cognitive Scientists will be able to show what structures are involved in memory transformation and how it occurs. Finally, matching electrophysiological measurements and the circuits involved with different behavioural observations will help us further understand the complex mechanisms of memory coding, storage, transfer and retrieval.

Conflict of Interest

The authors declare no competing interests.

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