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UPDATE ARTICLE

New frontiers in the study of memory mechanisms

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We review recent work on three major lines of memory research: a) the possible role of the protein kinase M-zeta (PKMzeta) in memory persistence; b) the processes of ''synaptic tagging and capture'' in memory formation; c) the modulation of extinction learning, widely used in the psychotherapy of fear memories under the name of ''exposure therapy''. PKMzeta is a form of protein kinase C (PKC) that apparently remains stimulated for months after the consolidation of a given memory. Synaptic tagging is a mechanism whereby the weak activation of one synapse can tag it with a protein so other synapses in the same cell can reactivate it by producing other proteins that bind to the tag. Extinction, once mistakenly labeled as a form of forgetting, is by itself a form of learning; through it animals can learn to inhibit a response. We now know it can be modulated by neurotransmitters or by synaptic tagging, which should enable better control of its clinical use.

Keywords: Memory; persistence; consolidation; synaptic tagging; extinction

Introduction

There have been many advances in the study of the mechanisms of memory in the past few years. Perhaps the most salient are: a) the discovery of a role of an atypical isoform of protein kinase C (PKC), protein kinase M-zeta (PKMzeta), in memory consolidation and persistence;[1,2] b) the wide acceptance and extension of the mechanism known as ''synaptic tagging'' or ''synaptic tagging and capture''[3,4] to a variety of memory forms[5,6] including extinction[7]; and c) the demonstration that extinction, now generally recognized not as forgetting but just as another form of learning,[8-10] can be modulated by several systems and procedures.[10] This should make it amenable to both psychotherapeutic and pharmacologic interventions.

These three discoveries open new vistas for the understanding and treatment of memory disorders. The three derive from hypotheses or findings published more than 10 years ago, which illustrates how research in this area relies on continuity in spite of major technological changes that take place all the time.[1,3,10] None of these discoveries would have been possible without the perhaps final agreement that long-term potentiation (LTP) is indeed the basis of memory consolidation at the cellular level in the hippocampus.[11-15] This had been repeatedly proposed by many to be the case in the 30 years that followed its original discovery in 1973 by Bliss et al. (see references[11,16-18]) and work on ''in vitro'' LTP models was widely hailed as representing work on the actual mechanisms of memory formation in vertebrates,[17,18] which eventually proved true. But the final agreement required the demonstration that the nature and sequence of the biochemical steps of hippocampal LTP were the same as those of memory consolidation in awake, behaving animals in tasks effectively mediated by this structure,[11,12] that the consolidation of those tasks is indeed accompanied by hippocampal LTP,[13-15] and that consolidation can be occluded by previous saturation of hippocampal LTP mechanisms.[13,15]

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A role for PKMzeta in memory

Clearly, then, hippocampal LTP is at the center of the initial, post-acquisition process of memory consolidation.[11-19] It has recently been shown to be one of the very few attributes of memory that is partly modulated by cholinergic transmission,[20] which explains the effect of pro-cholinergic drugs on memory impairments.

Memory consolidation is the process of formation of a memory archive in the brain. This takes place initially in the hippocampus, often with the concomitant participation of the entorhinal and posterior parietal cortex and the basolateral nuclear complex of the amygdala. The process takes 1-6 hours and involves the serial and parallel activation of several hippocampal protein kinase systems,[11,12,17] and the resulting stimulation of diverse cellular proteins including nuclear transcription factors which trigger DNA transcription, which is followed by protein synthesis in ribosomes[21] and coexists with the independent extra-ribosomal dendritic system mediated by mTOR (mammalian target of rapamycin), which uses pre-existent mRNAs.[22,23] The mTOR system is also triggered by protein kinases and by brain-derived neurotrophic factor (BDNF) (see below) and produces the GLUR1 subunit of the glutamate AMPA receptor, which is necessary for consolidation.[23] Due to its localization near synapses, the mTOR system is believed

to play a key role in the processing of proteins related to the processing of recent information by specific synapses, as is believed to happen in memory consolidation, which is accompanied and underlain by morphological synaptic changes.[11,12] The processes summarized above (protein kinase activation, protein synthesis, synaptic change) integrate what is now called ''cellular consolidation'' and cannot be delayed without loss; it has to occur immediately following acquisition.[11,24] An additional consolidation process, termed ''systems consolidation'', which is initiated simultaneously, takes place in the prefrontal cortex and other cortical regions, lasts for many weeks or even years, and frequently results in changes in the content of each memory, which can in many cases become falsified.[25]

After memories are consolidated in the CA1 region, they are stored in a long-lasting form (days, weeks, years) elsewhere, as attested by studies of humans or animals with anatomical or biochemical lesions of the hippocampus and its surrounding areas; the most famous and best studied human case is that of patient HM.[11,24,25] Subjects with those lesions can retain declarative memories for a few minutes or sometimes hours, but are unable to store them for longer periods; they can, however, remember facts and events that antedate the lesion, indicating that declarative memories do require the hippocampus early on but then must be stored somewhere else in the brain.[24-26] Recent evidence suggests that the secondary sensory cortices[27] and some prefrontal and parietal regions,[25,26] but not the hippocampus,[25] are sites of long-term memory storage.

Notwithstanding this, several recent studies have implicated the hippocampus in the initiation of "permanent" memory storage, in some cases through local biochemical changes.[28-33] These biochemical changes involve the production of local BDNF[28,29] and/or the local activation of a circadian cycle of simultaneous increases of hippocampal mitogen-activated protein kinase (MAPK) activity and cyclic adenosine monophosphate (cAMP),[30,31] and/or the triggering of a dual muscarinic and nicotinic cholinergic mechanism within the hippocampus,[32] or the participation of a hippocampal β-noradrenergic mechanism activated by mild stress, presumably that of the training experience.[33] The BDNF mechanism appears to be triggered by dopaminergic fibers from the ventral tegmental area acting on hippocampal D1 receptors.[30,31] Interestingly, all these mechanisms have been proposed to enter into play several hours after training, when the ensuing cellular consolidation process are already over,[28-35] and they are not mutually incompatible, which means they might occur simultaneously and eventually interact with each other in the fostering of memory persistence.

Perhaps in a different class, but not necessarily, is the suggestion by Sacktor et al.[1,2,36] of a role of the autonomously active, atypical PKC isoform PKMzeta in both memory consolidation and persistence. Regular PKC had been proposed as a key step in LTP generation - and, consequently, in memory formation - nearly three decades ago.[17,37] PKCs, including PKMzeta, are involved in the phosphorylation of a wide number of proteins, including membrane proteins, other kinases, receptors and nuclear transcription factors.[37] Inhibitors of PKMzeta infused into the hippocampus block both consolidation and persistence; the latter, even many days or weeks after the memories had been acquired.[2,36] The effect was originally described for the lengthening of the duration of hippocampal LTP and subsequently for hippocampus-based spatial memories.[1,2,36] Recent findings, however, indicate a completely different and in fact opposite role of PKMzeta in memory formation: its decrease correlates with an enhancement of the learning of familiarization to a new environment.[38] The overwhelming majority of papers mentioning a role of PKMzeta in memory, however, support a key role for this enzyme in memory persistence, at least for several weeks.[2,36] Inhibition of the enzyme rapidly erases memories acquired 1 day[1,2] or several weeks before.[2,36] The finding also applies to forms of neuronal plasticity other than LTP[39] and to many other forms of memory in invertebrates.[2,39]

It has been known for over a decade that the persistence of episodic declarative memories depends substantially on the degree of emotional alertness associated with its initial consolidation.[24,40,41] Thus, Americans are prone to remember details of where they were and whom they were with at the time President Kennedy was assassinated, whereas Brazilians tend to remember similar details of the time at which ace driver Ayrton Senna was killed, but neither can remember equally well incidents that occurred the day before or the day after such events. Perhaps the role of PKMzeta in the triggering of persistence is therefore related to its role (or to that of other PKCs) in memory consolidation, which has long been described.[11,17] Indeed, a role of regular PKC in the persistence of LTP over 3 days was described nearly 20 years ago.[37]

However, a role of PKMzeta or PKC in consolidation would mingle with its role in promoting persistence, and if this were so, the other persistence mechanisms that have been postulated (BDNF-mediated, MAPK/CaMKII-dependent, noradrenergic, cholinergic (see above) may just be accessory or alternative.

More research into this area is desirable. In particular, the exact role of PKMzeta in consolidation and persistence should be more clearly laid out. A prolongation of the former into the time in which the latter operates could be as self-defeating in terms of memory persistence, as remembering where we parked our car yesterday when looking for it when we leave our office today, or remembering how we reacted to a cake we ate at 3 p.m. today instead of how we should react to the tiger that attacked us 1 hour after the cake and is attacking us again now.

It bears stressing that the wholesale, uncritical acceptance of a role for PKMzeta in memory persistence collides head-on with all we have learned from years of research on patient HM and others with hippocampal lesions that came after him,[24-26] mainly, that the hippocampus ceases to play a role in memory maintenance or persistence shortly after cellular consolidation is over. Patients with hippocampal lesions can remember

declarative memories from weeks before the lesions but are unable to form new memories of that kind.[25,26] Just how long the PKMzeta mechanism remains operational for each memory remains to be established with much more precision than that emanating from the data published on that enzyme so far. If it stays on for weeks, this would not be incompatible with what we learned from HM.[26] If it has to stay on for months or years, its role would be hardly credible, inasmuch as memories are made constantly and animals would find it impossible to tell one from the other. Perhaps the most parsimonious assumption would be that the PKMzeta molecules that are altered remain in this state for a few weeks at the most, and are located at the synapses specifically used by each one of those memories. The two human hippocampi together have at least 400 million pyramidal cells, each receiving about 10,000 synapses, which makes it an apparatus with potentially formidable, though not infinite, synaptic processing properties. If specific connections between the hippocampal synapses that are involved in consolidation[28-33] and those that house their more permanent storage forms[25,27] exist, they must be modest in size and number.

Synaptic tagging as a physiological process in memory formation

In 1997, Frey and Morris proposed a mechanism whereby weak LTPs that last only 30 min or so could be turned into full-fledged processes lasting several hours by other LTPs developed in other synapses of the same neuron.[3] The mechanism involves tagging of the synapses participating in the weak LTP by local proteins and the capture by these tags of other proteins, called plasticity-related proteins (PRPs), generated at the synapses involved in the other LTP process. This mechanism has been called the "tagging and capture" hypothesis[3,4,6] and has been found appropriate to explain both the switch from an early, brief form of LTP to a long-lasting (days, weeks) form[3,4] and the facilitation of "weak" memories by simple exposure to a novel experience.[4-6,42-44] In the latter case, it is often called "behavioral tagging."[5,6] The original learning would produce a protein that tags a set of hippocampal synapses so that the tag would then capture the PRPs generated by novelty (or some other learning, or a second LTP) in other synapses of the same cells. This would explain the well-known associative property of learning, particularly of recently made memories. Clearly, synaptic tagging may explain not only the associative property of memory, but also the interactions between memories of different content but close in time.[3,6,42-44]

One recent paper has proposed that PKMzeta may be one of, if not the key PRP to be captured by the tags left by "weak" learning.[45] Another paper, without going as far as advancing this proposal, has nevertheless suggested a key role for PKMzeta in the persistence of the tagging and capture process.[46] Many other papers have suggested a variety of other PRPs.[4,6] There is usually a time constraint of about 1 h between tagging and capture.[3,46] This time constraint is particularly evident in behavioral tagging (i.e., that between a "weak" memory trace and a novelty).[5,42-44,47] A metaplasticity process has been suggested to activate PKMzeta and lengthen this tag-to-capture interval considerably.[46] It remains to be determined, however, whether such lengthening can occur physiologically and, if it does, whether it would be useful for the associative property of memory formation, which is usually known to be quite brief.[47]

A possibility that cannot be dismissed without experimental data is that the activity of PKMzeta is not the cause of persistent memories but a consequence thereof, much as fever is not a cause but rather a consequence of infectious disease. Unless proven otherwise, this remains a hindrance to accepting that PKMzeta is at the source of memory persistence.

The modulation of extinction

Extinction was originally described in the early 20th century by Pavlov[47] as the process by which the repetition of a conditioned stimulus in the absence of any further reinforcement leads to the inhibition of the conditioned response. For example, if a tone which had been paired with food is then repeated alone several times, the salivation that had developed to the tone as a conditioned response gradually disappears. Extinction was introduced into psychiatry by Freud in the 1920s, who applied it to the successful treatment of phobias under the name of "habituation",[48] a name which was not accepted by most because it designates a different process: the gradual inhibition of an unconditioned response.[47,49] In recent years, often under the name of "exposure therapy", extinction has been also successfully applied to the treatment of posttraumatic stress disorder (PTSD).[9,50,51] Extinction can reverse either spontaneously[8] or by reintroduction of the reinforcement: just one tone-food pairing can fully reinstate the original Pavlovian conditioned salivation reflex.[47]

If a behavioral procedure is to be used in therapy, it should be amenable to modulation, and therefore manageable by the therapist. If it were so rigid that once set into action it cannot be stopped, accelerated or decelerated, it would be psychologically dangerous to use it; a misapplication or an unwilling error could lead to serious long-lasting consequences. We have recently found that extinction in two different aversive paradigms in rats can indeed by modulated by eight different treatments infused shortly after the first of two sessions of extinction in three different areas of the brain: the ventromedial prefrontal cortex, the basolateral amygdala and the CA1 region of the hippocampus.[10] These three areas have been previously shown to be effectively involved in the generation of extinction learning in the two tasks, both by the occurrence of protein synthesis in them when extinction learning is consolidated and by other parameters.[52-54] The treatments found to modulate extinction are known to act upon dopaminergic, noradrenergic, histaminergic or glutamatergic synapses,[10] i.e., four typical modulatory sets of synapses, and some of them have been tried therapeutically to good effect in

many situations that do not involve extinction learning, so side effects would presumably be few.

In addition, we also found that a brief exposure to novelty (see above) may enhance extinction if presented 2 h before or 1 h after the first of two sessions of extinction; i.e., at the time when recent extinction learning is being consolidated.[7]

These findings obviously open an entirely new vista over the use of ''exposure'' (extinction) therapy of PTSD. Once initiated, treatment can be accelerated or decelerated according to the reaction of the patient. To some, this form of therapy may appear intolerable, especially in the first few sessions; to others, who want to get rid of their syndrome quickly, it might be too slow. It would certainly be practical to modulate the speed of treatment by drug administration or by the interposition of other psychological stimuli, such as the perception of a novelty.

A reflection

It is often said that memory research, or research in neuroscience as a whole, has progressed more in the last five than in the preceding five or 50 years. This is because there are many more trained scientists dedicated to these overlapping areas now than ever before, and the techniques at our disposal are better and much more accurate now than they were a few years ago. However, in the account given above of the three areas of memory research that perhaps stand out today at their frontiers, it is clear that all derive from findings and ideas originated several decades ago.

Modern memory research probably began with the careful analysis of the results of the brain damage suffered during bilateral temporal lobe surgery by the famous patient HM in 1953, and of the overwhelming irruption of molecular biology in life sciences research starting with the discovery of the double helix in 1954. Those were times of great innovation in biology; advances in neuroscience since then have been enormous, and the field of memory was changed forever. Later, brain imaging and sophisticated molecular pharmacology added to the methods of analysis and paved the road for the findings and concepts of today. It is good to reflect on this chain of events and realize that, although the findings summarized herein are new, they are based on ideas and other findings dating back several years. A role of PKC in memory was first described in the 1970s,[17] the idea of synaptic tagging was introduced in 1997,[3] and extinction was discovered over one century ago.[47]

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Disclosure

The authors report no conflicts of interest.

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