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FUNCTION OF THE HIPPOCAMPUS IN MEMORY FORMATION: DESPERATELY SEEKING RESOLUTION

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Contents

Abstract

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1. Despite considerable efforts and successes investigating the function of the hippocampal formation in memory processes, there are still numerous elusive key issues. Some of them will be addressed in this review.
2. We will argue that recent evidence supports hippocampal participation in several memory processes, such as encoding, short-term and long-term consolidation and retrieval. While some processes, for example encoding and short-term

consolidation, have been the subject of detailed investigations, at least for specific and repeatedly used behavioural paradigms, there appears to be considerable lack of information with respect to other processes, for example long-term consolidation.

3. Although the existence of long-term consolidation is not at debate here, there is only very fragmented information as to the cellular processes enabling long-term consolidation. Recent ample evidence now suggests a potential role in metabotropic glutamate receptors, and more specifically the phospholipase C-coupled receptor 5, in long-term consolidation.
4. The hyperexpression of receptor protein was limited to CA1 indicating a specific role of this brain region in the consolidation of memories.
5. Future work should further explore this important issue especially since long-term consolidation appears to be a necessity for permanent storage of information, and may thus engage memory mechanism that fail during ageing and dementia.

Keywords: consolidation, encoding, hippocampus, memory formation, metabotropic glutamate receptors, phases of memory

Abbreviations: 1-aminoindan-1,5-dicarboxylic acid (AIDA), a-amino-3hydroxy-5-mwthyl-4-isoxazolepropionic acid (AMPA), calcium response element binding protein (CREB), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), diethyldithiocarbamate (DDC), γ-amino-butyric acid (GABA), glutamate receptor 1 (GluR1), long-term depression (LTD), long-term potentiation (LTP), magnetic resonance imaging (MRI), metabotropic glutamate receptor 5 (mGluR5), metabotropic glutamate receptors (mGluRs), N-methyl-D-aspartate (NMDA), perforant path (PP), tetrodotoxin (TTX)

1. What to Expect from this Viewpoint Article

When studying the literature on hippocampal function, we became aware of an enormous amount of detailed knowledge that has been accumulated until today. It has certainly increased our understanding of its function, and will facilitate future work. Surprisingly, however, few attempts have been published proposing new issues and developing novel and testable hypotheses. Our main agenda therefore is *not* to provide the reader with detailed and extensive background information. Rather, we attempt to develop some new ideas of how the hippocampus might work and present preliminary support for our hypotheses. Also, in raising some, as we find, exciting issues, we shall try to develop experimental designs for supportive experiments. The paper is thus meant to inspire psychologists, pharmacologists and physiologists alike to work on *concepts* rather than *details*.

2. What do We Need the Hippocampus for? A Brief Introduction

In mammals the formation and storage of declarative (Squire, 1987) or propositional (Tulving, 1993) memory depends on a system of anatomically related structures within the medial temporal lobe and on its interaction with the neocortex (Squire 1992; Cohen and Eichenbaum, 1993). With respect to memory formation, the hippocampus comprises a core structure of the medial temporal lobe and its functional integrity appears to be a prerequisite for normal acquisition of information about relationships, combinations, and conjunctions among and between stimuli. Such associations are then retained across time. Two contending theories consider the medial temporal lobe, and more specifically the hippocampus (cornu ammonis, dentate gyrus and subiculum), to be either the place for temporary storage of to-be-consolidated information (Squire, 1992 and citations therein), or as the locus of permanent information storage through multiple memory traces (Nadel and Moscovitch, 1997). While evidence from animal experiments supports the 'Squire' view (Bontempi et al., 1999; Kim and Fanselow, 1992; Zola-Morgan and Squire, 1990; Anagnostaras et al., 1999), there appears to be at least some evidence for long-term storage from human case studies (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). It is thus important to exactly determine for how long the hippocampus participates in memory formation.

Anatomical studies as well as physiological recordings made in freely moving animals, mainly rats, provide some first hints. Witter et al. (1989) have summarised intrinsic and extrinsic connections of the hippocampus. Entorhinal input via perforant path (PP) is segregated and fibres arising from the lateral entorhinal cortex form the lateral PP and are part of a predominantly sensory circuit that also conveys considerable information from the perirhinal cortex with, among other sensory inputs, olfactory content. Activity of this sensory input would be required during acquisition and recall of information. By contrast, fibres arising from the medial portion of the entorhinal cortex form the medial PP. This pathway reflects the limbic component and issues highly processed information to the hippocampus. Such information might be substantially involved in memory formation processes like consolidation or storage. This segregation of channels is maintained within the hippocampus and in its specific output pathways returning to the rhinal cortex.

2.1. Insights from the Anatomy and Physiology of the Hippocampus

Physiologically there are numerous rhythms that have been identified within the hippocampal network. Buzsaki (1989) proposed a two-stage model of information processing for the hippocampus. During acquisition (exploration for example) dentate granule cells discharge in theta waves (5-12Hz) while pyramidal cells in CA3 and CA1 are relatively quiescent. With a decrease in exploration the granule cell theta rhythm fades and is replaced by synchronised activity in CA3 and CA1 consisting of sharp waves (brief bursts of discharges of up to 200Hz). These sharp waves entrain CA3/CA1 discharges and this oscillation is then transmitted back to the entorhinal cortex. A possible scenario binding hippocampal output with neocortical activity may use gamma frequency oscillations within this network (Chroback and Buzsaki, 1996). As assessed by the authors this mechanism could support an "off-line" memory consolidation process. This hypothesis is further strengthened by the finding that a single burst is capable of generating either LTP or LTD in CA1. The sign of synaptic change is produced by the timing of stimulation with respect to the phase of the oscillation of the theta rhythm (Huerta and Lisman, 1996).

To give this physiological observation behavioural relevance, one could thus argue that specific encoding of new information requires the integrity of dentate gyrus granule cells. Processes of memory consolidation, either short-term or long-term, by contrast, should depend on the network activity of the hippocampus proper (CA1-CA3) in conjunction with selected output channels either back to the entorhinal cortex or into a motor loop via nucleus accumbens. It is obvious that given the anatomical proximity of the brain structures in question, selective lesions, pharmacological or temporary inactivation of dentate versus CA1 or CA3 are extremely difficult to achieve. A recent attempt made use of diethyldithiocarbamate (DDC) to selectively and temporarily inactivate the mossy fibre-CA3 projection in mice (Lassalle et al., 2000). When trained in a reference memory task in the Morris water maze, animals were impaired when CA3 was switched off prior to learning, but not when switched off immediately post-training, implicating the mossy fibre pathway in new learning, but not in memory consolidation or retrieval.

This scenario may not be independent of the information content; event-related memories require hippocampal integrity, procedural memories *may* not. Furthermore, it is conceivable that different stages of memory expressed through specific physiological

responses are brought about by activation of independent pharmacological mechanisms within the same hippocampal network.

A word of caution may be in place here. What we mean when we talk about consolidation is memory lasting for one day or more. Short-term memory (up to 2 or 3 hours in animals) or working memory are not at dispute. Apart from the fact that both working and short-term memory may engage different anatomical substrates compared with long-term memory, elegant recent work by Izquierdo and colleagues (1997, 1998a, b) has provided compelling evidence for separate pharmacological mechanisms underlying the different forms of memory. Such data are in line with the 'single trace – dual process' view of memory formation (Gold and McGaugh 1975). With respect to the hippocampus, it appears that blockade of dopamine D1 receptors enhanced short-term memory without affecting long-term memory while norepinephrine has the opposite effect. Similarly, the metabotropic glutamate receptor antagonist 1-Aminoindan-1,5-dicarboxylic acid (AIDA) facilitated short-term, but impaired long-term memory when given intraperitoneally in rats (Christoffersen et al, 1999).

2.2. Hippocampus and Encoding

From a vast amount of literature published on lesions or pharmacological inactivations, one would expect compelling evidence for a hippocampal role in the encoding of new information. A closer look, however, shows that direct evidence for such function is rather scarce. Why? Let us consider drug studies first. The aim of most pharmacological interventions is to selectively interfere with memory formation by either blockade or activation of specific receptors, enzymes, transcription factors or genes. One important aim thereby is to induce *no* learning or acquisition deficit, but to obtain amnesia when testing for retention. Such studies therefore target memory consolidation processes and not acquisition. Similar aims underlie behavioural studies using working memory protocols such as delayed matching or non-matching to sample/place. As has been firmly established now, the hippocampus is important only if longer delays are employed and drugs interfering with memory formation do not affect very short delays (Hampson and Deadwyler 1999; Steele and Morris 1999). This then clearly establishes that the

hippocampus and the respective pharmacological system under investigation are not essentially part of the encoding of new information.

So can we learn more from lesion studies? A general problem here is that lesions often result in cross motor deficiencies – hippocampal lesions can cause hyperactivity (Good and Honey 1997 for a recent example), which may bias performance in many behavioural tasks, and this might cause considerable difficulties for the interpretation of the data. Similar problems can actually occur when drugs are systemically administered or when genes are knocked out (Conquet et al., 1994; Aiba et al, 1994). Furthermore, what is measured after a lesion is the amount of compensation within the central nervous system due to the complete lack of a particular brain structure. An example should demonstrate this point. Numerous lesion studies, specifically those using neurotoxic techniques (Jarrard 1989) aimed at complete removal of the hippocampus have resulted in learning deficits (Morris et al., 1990). But as is clear from recordings of single units, the hippocampus is not a uniform structure and cells differ with respect to their physiological properties in that place cells of the dorsal hippocampus have much more confined place fields as compared to those in the ventral hippocampus, where place fields are more disperse. As a result, lesioning the ventral hippocampus had no measurable consequence on acquisition learning or retention of a spatial paradigm in the Morris water maze (Moser et al., 1993). By contrast, dorsal hippocampal lesions completely abolished learning and it was argued that the dorsal but not ventral hippocampus was involved in the encoding of new spatial information. A follow-up study, however, provided evidence, which made this interpretation highly questionable. Animals were trained in the water maze and the ventral hippocampus was lesioned 24 hours later. After recovery, sham-lesioned controls perfectly remembered the location of the hidden platform, while ventral hippocampus-lesioned animals were impaired (Moser and Moser 1998). These results suggest that at least some information had been encoded in the ventral hippocampus during acquisition. Although the exact function of the ventral hippocampus in spatial learning still remains elusive, this example illustrates the interpretational difficulties arising from lesion studies, but it points towards an involvement of the hippocampus in learning.

A somewhat different technical approach is the temporary and localised inactivation of specific brain structures. Possible compounds to be applied include the local anaesthetic lidocain, the sodium channel blocker tetrodotoxin (TTX), activators of inhibitory neurotransmission like γ-amino-butyric acid (GABA) or muscimol, or specific blockers of fast

synaptic transmission such as CNQX or the recently introduced water soluble LY 326325. Each compound has specific properties, which provide advantages and disadvantages depending on the intended use. For instance TTX is relatively short lasting (few minutes) but not very selective as it does not spare fibres of passage. Lidocain on the other hand lasts longer, spreads further from the infusion site and also affects fibres of passage. Agonists of GABA receptors or blockers of AMPA receptors are both more specific, but their course of action is prolonged and thus more difficult to control. They may prove useful in case of long-lasting acquisition protocols using the radial or the water maze. By means of LY 326325 chronically infused into hippocampus, we have recently provided compelling evidence for a role of the hippocampus in encoding of novel spatial information (Riedel et al., 1999). Interference with consolidation was prevented by removal of the minipumps before the last training session in the knowledge that clearance of the drug would take at least 6-8 hours.

Considerable advances have been yielded by the development of functional scanning techniques in humans measuring brain activity during different phases of memory formation. With respect to the hippocampus, however, these studies have predominantly focussed on its involvement in recall (Squire 1992 for example). And although it had been envisaged that the hippocampus is important for encoding of declarative memory, strong evidence was only reported very recently. Two independent groups found significant correlations between the activity within hippocampus during encoding and intentional (Fernandez et al, 1998) or free word list recall (Alkire et al., 1998) using functional MRI or positron emission tomography, respectively. Such experiments may provide the starting point for future advancements underpinning the role of hippocampus in the encoding of different forms of memory.

3. Hypotheses

Following encoding, it is now consequent to evaluate the function of hippocampus in memory consolidation. We shall follow this logic and try to develop two novel hypotheses. The first one deals with the question: how long is the hippocampus involved in memory consolidation? As will be outlined, current results support the notion for several phases of memory consolidation allowing specific interference at various time points post-training. We shall argue for an as yet not explored very late consolidation phase, which in rats may

continue for days and weeks with the hippocampal circuitry continuously entraining cortical structures until final storage has been achieved. The second hypothesis is concerned with the possible physiological/pharmacological mechanisms underlying this consolidation phase and we shall introduce recently reported data suggesting a role for metabotropic glutamate receptors in this late consolidation phase.

3.1. Multiple phases of memory consolidation

Based on current physiological and, more importantly, pharmacological evidence, the training event which initiates encoding of information also triggers the start of processes with a longer time course. We here propose the existence of multiple phases of consolidation with different time courses each.

But before providing some more details, we need to define when consolidation takes place. It is generally believed that in order to enable long-term episodic memory, the information is temporarily stored in the hippocampus where it remains vulnerable to interference. Via a slow read-out process, the information is transferred into other brain structures where the memory is established and no longer vulnerable to interference. This slow read-out is termed consolidation (Mueller and Pilzecker, 1900). A distinguishing characteristic of long-term memory is its sensitivity to inhibitors of protein-synthesis during consolidation (Davies and Squire, 1984; Stork and Welzl, 1999). Work performed in the 60's an 70's consistently reported that inhibition of protein synthesis is required around the time of training. Application of cycloheximide or anisomycin several hours post-training were not effective. These data suggested that training induced the rapid induction of protein-synthesis, which maintains the memory trace while it is still vulnerable to interference. Several follow-up studies have now provided compelling evidence for two protein synthesis-sensitive consolidation phases.

In their initial work, Grecksch and Matthies (1980) trained rats in a brightness discrimination task in a Y-maze and applied anisomycin at several time points prior of after training. The resulting time course showed a biphasic inhibition of memory when anisomycin was administered either shortly after or 4-6 hours post-training, but no effect

was found at intermediate time points. These data have subsequently been confirmed for one-trial avoidance learning in chicks (Freeman et al., 1995) and contextual conditioning rats (Bourtchouladze et al., 1998; Quevedo et al., 1999). These data suggest at least two different 'waves' of protein synthesis subsequent to learning, which are necessary to establish long-term memory. We refer to these two waves as *immediate* and *intermediate* waves of protein synthesis-dependent consolidation (Fig. 1).

From our recent work using temporary inactivation by means of LY 326325 (Riedel et al. 1999) we propose the existence of another protein synthesis-dependent wave of memory consolidation within the hippocampus. The hippocampus was inactivated as late as 5 days post-training for several days and was switched back on prior to the probe trial. Animals treated in this manner were amnesic as to the spatial location of the training platform. Although we have not directly tested the hypothesis, that amnesia is due to a lack of protein synthesis while the hippocampus was switched off, it should be intuitively clear that a reduction in cellular activity would be accompanied by a reduction in the overall protein synthesis. In addition, we have preliminary protein measurements that can be interpreted in support of this hypothesis (see the following sections).

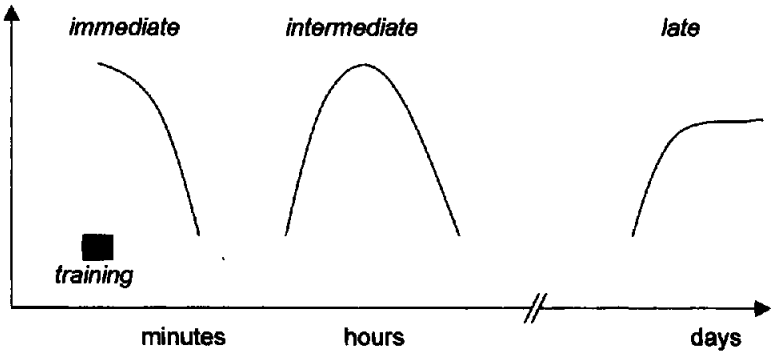

Fig. 1: Hypothetical time-course of protein synthesis-dependent waves of memory consolidation.

In addition, numerous other mechanisms have been described that are active in the interim phases while memory formation is insensitive to protein synthesis inhibitor exposure. In many cases their time courses have not been established in great detail or their activation pattern is only short-lasting. What is of potential interest here and relevant

for the following section is the question: Which are the proteins made during the respective waves?

3.2. Consolidation and Novel Proteins for Memory

In the following section, we intend to focus on the proteins, which have been described to increase/decrease as a consequence of learning. Given that the protein synthesis dependence of long-term memory has been known for quite some time, one might expect a long list of proteins to be available corresponding to the above mentioned waves. A closer look however shows, that research has concentrated on the identification of receptors and their intracellular enzyme cascades that eventually will funnel into activation of genes (Riedel and Micheau, 1999). The respective cascades include enzymes such as kinases and phosphatases (Micheau and Riedel, 1999; Riedel, 1999), transcription factors such as CREB (Lamprecht, 1999), and immediate early genes (Tischmeyer and Grimm, 1999).

What we are concerned with, on the other hand, is the learning-induced increase in receptor proteins. Why? Although it is helpful to identify increases in the activity of enzymes or increases in the amount of intracellular proteins per se, there are multiple transmitter systems active within the hippocampus. Many of these transmitters stimulate ionotropic and metabotropic receptors activating the very same intracellular cascades. Moreover, there is extensive cross talk between these intracellular cascades making it difficult to determine the cellular origin of the signal that has led to any alteration. For simplicity reasons, we shall make the assumption that a particular learning condition will activate a very specific set of neurones within hippocampus and therefore a very specific set of pre- and post-synaptically expressed receptors. Changes in these systems could temporarily store the information as has been proposed to being the major role of the hippocampus (Squire, 1987; 1992). If the information is stored and reverberated within the hippocampal network it seems likely that the same excitatory responses will activate the same subset of neurones and receptor proteins. As a consequence, one might expect specific alterations of receptor proteins to take place at the specific consolidation-dependent sites within hippocampus. Alterations in receptor proteins would enable facilitated reverberation of exactly the same information for prolonged periods of time (Hebb, 1949).

Experiments addressing this kind of problem thus would measure expression of receptor proteins within circumscribed areas of the hippocampus. Inspired by the observation that induction of long-term potentiation (LTP), a cellular model of synaptic plasticity resembling features believed to underlie memory formation (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999), leads to increased AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) responses (Davies et al., 1989; Sergueeva et al. 1993). This data suggested either increased affinity of existing receptors or an increase in receptor number. Since the increase in AMPA responses following LTP induction appear after few minutes, synthesis of novel protein is unlikely and it has been found more recently to be due to unmasking of AMPA receptors in silent synapses (Isaac et al., 1995).

Behavioural experiments have been conducted using three paradigms, eye-blink conditioning, contextual conditioning and inhibitory avoidance learning, and receptor expression has been determined post-training. Compared to several control groups, it was consistently reported that learning induced selective and region-specific increases in AMPA binding within hippocampus Tocco et al., 1991; Cammarota et al., 1995). Evaluation of the full time course revealed enhanced AMPA binding in CA1 shortly after training (0.5-2hrs) followed by a longer lasting increase in CA2 and CA3 (0.5-24hrs and 0.5-48hrs, respectively) and in dentate gyrus (2-48hrs) (Fig. 2). The early CA1-specific increase in AMPA binding coincided with an increase in GluR1 subunit expression (Bernabeu et al., 1997; Cammarota et al., 1998). In CA1, enhancement of dopamine D1 receptor binding has been shown 3-6 hrs post-training (Bernabeu et al., 1997).

What do these data mean? First, the reversibility of the increase in AMPA reactivity combined with the lack of change in the control groups strongly suggests a relation to the learning event. Second, it appears that AMPA receptor mediated responses increase in hippocampus during the first 1-2 days after learning, and this may facilitate reverberation of the signal and entrain other brain structures in which the memory is eventually stored. Third, the increase in GluR1 expression suggests involvement of protein synthesis. Whether novel protein is expressed within 30 minutes remains to be clarified, but for later enhancements of AMPA responses in CA3 and dentate, expression of novel receptor proteins is indicated. Forth, the failure to find an increase in AMPA binding in hippocampus 7 days post-training supports the view that other mechanisms may exist that enable consolidation with a longer time course.

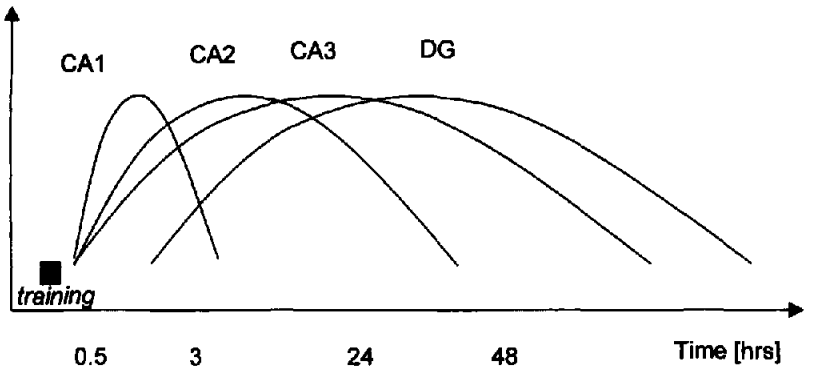

Fig. 2: Schematic outline of the time-course of increase in AMPA-receptor binding (ordinate) in hippocampus following learning based on data published by Cammarota et al. (1996). The early increase in AMPA binding in CA1 correlates with a significant increase in GluR1 immunoreactivity (Bernabeu et al., 1997).

A somewhat longer time-course has been described for metabotropic glutamate receptors (Riedel et al., 2000). Antibodies were used directed against phospholipase C-coupled group I mGluRs and Western blots showed a time-and region-specific increase in receptor proteins in hippocampus. Metabotropic GluR5 was increased in CA3 24 hrs, but not 10 days post-training. By contrast, mGluR5 was overexpressed in CA1 and dentate gyrus 10 days, but not 24 hrs post-training (Fig. 3). Combined with the recent observation, namely that prolonged inactivation of the hippocampus 5-12 days post-training interrupts memory consolidation (Riedel et al., 1999), these data suggest that in contrast to AMPA receptors, mGluRs in hippocampus may contribute much more to the late phase of memory consolidation. Given the direct coupling with intracellular enzyme cascades, this should be expected, because it enables direct activation of cellular pathways that mediate long-term metabolic changes. It is exactly this long-lasting reverberation that is required for the slow but continuous consolidation of the memory trace. By contrast, AMPA receptors mediate fast synaptic transmission and thereby only modulate intracellular protein cascades indirectly.

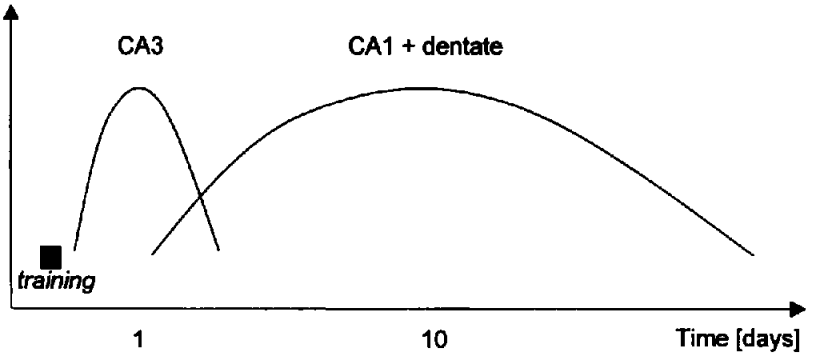

Fig. 3: Hypothetical time-course of the increase in metabotropic glutamate receptor 5 expression level (ordinate) in hippocampus following learning based on data published by Riedel et al. (2000).

Although there is continuous activation of AMPA receptors during the first days post-training, the full time course and activation pattern of other mGluR subtypes needs determination. It should be noted that although the activation of N-methyl-D-aspartate (NMDA) receptors is a key event in many learning processes and models of synaptic plasticity, a learning-induced increase in NMDA receptors has not been reported so far.

4. Conclusions

We here propose at least three protein synthesis-dependent waves of memory consolidation that take place within hippocampus. These waves lead to the production of many novel proteins. Expression of new receptor protein may be particularly important as they can be used to maintain input-specific activation of the assembly that has been active during learning. With respect to the consolidation of the memory trace, we propose that increases in AMPA receptor expression may be the products of *immediate* and *intermediate* waves of memory consolidation over minutes or days. Longer lasting memories with extended consolidation periods, in addition, draw on a third *late* wave. Metabotropic glutamate receptors are believed to be a product of this late wave and enable long-term consolidation of memory.

Future experiments should address this issue in more detail and take also into account the existence of other transmitter systems and their receptors. As by today, all we know is the localisation of the changes within hippocampus. It would, however, be instructive to establish the exact locus of the transient overexpression in order to develop refined models that will also take into account the physiological properties of all intrahippocampal neuronal and non-neuronal elements.

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