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Different molecular cascades in different sites of the brain control memory consolidation

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To understand cognition, it is important to understand how a learned response becomes a long-lasting memory. This process of memory consolidation has been modeled extensively using one-trial avoidance learning, in which animals (or humans) establish a conditioned response by learning to avoid danger in just one trial. This relies on molecular events in the CA1 region of the hippocampus that resemble those involved in CA1 long-term potentiation (LTP), and it also requires equivalent events to occur with different timings in the basolateral amygdala and the entorhinal, parietal and cingulate cortex. Many of these steps are modulated by monoaminergic pathways related to the perception of and reaction to emotion, which at least partly explains why strong and resistant consolidation is typical of emotion-laden memories. Thus memory consolidation involves a complex network of brain systems and serial and parallel molecular events, even for a task as deceptively simple as one-trial avoidance. We propose that these molecular events might also be involved in many other memory types in animals and humans.

Introduction

One-trial avoidance has been widely used for the study of memory consolidation. There have been many successful inferences from this task to other forms of memory, especially those of fear-motivated learning and spatial tasks. One-trial avoidance corresponds to many important examples of learning in humans, such as not to stick your fingertips into electric plug sockets, to look right rather than left when crossing a street in London, and to refrain from entering a suspicious-looking neighborhood.

The sequence of molecular mechanisms underlying long-term potentiation (LTP) in the CA1 region of the hippocampus has been proposed to underlie memory consolidation in that region [1–8]. This was shown to be indeed the case for one type of memory: one-trial avoidance learning [9,10]. However, at the same time, different sequences of molecular changes in other brain regions are also crucial for memory consolidation in this and other tasks [9–18]. The main difference between the molecular changes in the hippocampus and the other structures (the basolateral amygdala, and the entorhinal and parietal cortex) is their timing and sequential order [9–11]. Timing among its diverse underlying molecular events is a key factor in the build-up of LTP maintenance [1,4,10] and, as shown elsewhere [9–14] and discussed here, in the build-up of consolidation. The sheer number of connections within and among various brain structures in LTP and in memory formation is the reason why these processes are so complex [1,4,9,10], and why it is difficult to schematize them. Attempts have been made to devise schemes or blueprints for LTP [1,4] and memory [2,3,9,10]. However, by the end of this article we hope to have persuaded readers that memory consolidation requires not only LTP (or a process very much like LTP) in the hippocampal CA1 sub-area but also different sequences of the same or of related signaling pathways in other cortical areas and the amygdala [9,10,17].

What is memory consolidation?

Most neuroscientists view consolidation as a process lasting a few hours through which memories are transformed from a labile into a more stable state [1–14]. However, several authors favor the view that there is also another form of consolidation that lasts for many days or months, or even a lifetime [18]. No doubt memories can accrue or lose information over prolonged periods [9,10]. However, over days, months or years there are oscillations in the rate of extinction or forgetting, an incorporation of new and related short-term memories (STM) or long-term memories (LTM) [19–21] (including falsifications of the original memories [18]), and eventually relearning and reconsolidation [16–25]. Indeed, memories are made labile just by their retrieval [23].

Here, we will refer only to the more 'classic' form of consolidation that lasts a few hours [9,10,18,20,23]. For discussion of the alternative, 'prolonged consolidation' view, see Refs [10,16–25].

Why one-trial avoidance

One-trial step-down or step-through inhibitory ('passive') avoidance in rodents [9,10,18], or one-trial peck avoidance in young chicks [19,20], has long been a favorite model for

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biochemical and pharmacological studies of memory. In the rodent models, the animals learn that stepping down from a platform or stepping through a door is followed by a footshock; on subsequent exposures to the task they will stay much longer on the safe platform or on the safe side of the door before eventually stepping down or stepping through. In the chick model the animals learn to abstain from pecking a bead whose taste is bitter. Usually one trial is enough to establish a long-lasting memory of these tasks [9,10,18–20].

One reason for their popularity is the brief nature of the training procedure: a single fast association is made between a movement (stepping down or stepping through in rodents, pecking in chicks) and an aversive stimulus (a footshock in rodents, a bitter bead in chicks). The association takes place in seconds, as does LTP induction [9,10]. Thus in one-trial avoidance tasks, the onset of memory consolidation can be determined with precision [10]. This is not the case in other learning procedures, particularly multiple-trial tasks, in which each successive trial involves not only STM and LTM consolidation [21,22] but also retrieval, extinction, relearning and reconsolidation [23]. In multiple-trial tasks, pharmacological effects or biochemical measures observed could in principle be linked to any of those memory stages; there is no direct way of dissecting one from the others as in one-trial avoidance [23–30].

The second reason for the popularity of one-trial tasks is that, with remarkably few exceptions, the associated pharmacology of the rodent hippocampus and basolateral amygdala [9,10,17,18] and the biochemical effects of training [9,10,18] yield very similar results to those obtained in many other memory tasks (e.g. conditioned fear and spatial memory tasks). The same is true of the corresponding areas of the chick brain [19,20]. Therefore, much of what we know now about memory mechanisms has actually derived from observations of one-trial avoidance [1,9–11,18–22].

Many studies using injections of specific receptor blockers or enzyme inhibitors into a given brain structure have shown that the CA1 region of the hippocampus is essential for consolidation of one-trial avoidance [9,10,15,31,32]. However, the hippocampus has bidirectional links with the septum [33], the entorhinal cortex [26,27] and, through the latter, with other regions of the cortex and the amygdala [9]. It is difficult to believe that physiological events can happen in the hippocampus without reflecting on the activity of its connections and vice versa. Reversible blockade of function in any of these structures at different times relative to training disrupts memory as deeply as it does in the hippocampus [9,17,28,29,34]. Thus, memory formation is a complex process that requires different brain systems acting in concert [9,10,17,30]. This article reviews and comments these findings. (In all the tables we present, we refer to doses that were the most effective among those used in every case; full details of doses used can be found in the listed original papers.)

Main molecular events in CA1 LTP and in the consolidation of one-trial-avoidance memory

The main events in CA1 during consolidation of one-trial avoidance involve, like those in CA1 LTP [1–6,29], the initial activation of AMPA, metabotropic and particularly NMDA glutamate receptors [2,5,7,9,32–36]. This causes an increase of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) [1,5], followed by an enhancement of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) activity in the first 60 min [7,37–39], which leads to phosphorylation of AMPA receptors [39,40] and a prolonged increase in [^{3}H]-AMPA binding to the CA1 region [41,42]. As a consequence of the $[Ca^{2+}]_i$ increase, both in LTP [43] and in one-trial avoidance, the activity of various protein kinase C (PKC) isoforms increases together with phosphorylation of its substrate presynaptic growth-associated protein 43 (GAP-43) with a peak at 30 min [44–46]. GAP-43 is involved in mobilization of glutamate-containing synaptic vesicles to the presynaptic membrane [43], which has been postulated to have a role in CA1 both in LTP and in memory formation. In addition, PKC is important for the phosphorylation of glutamate

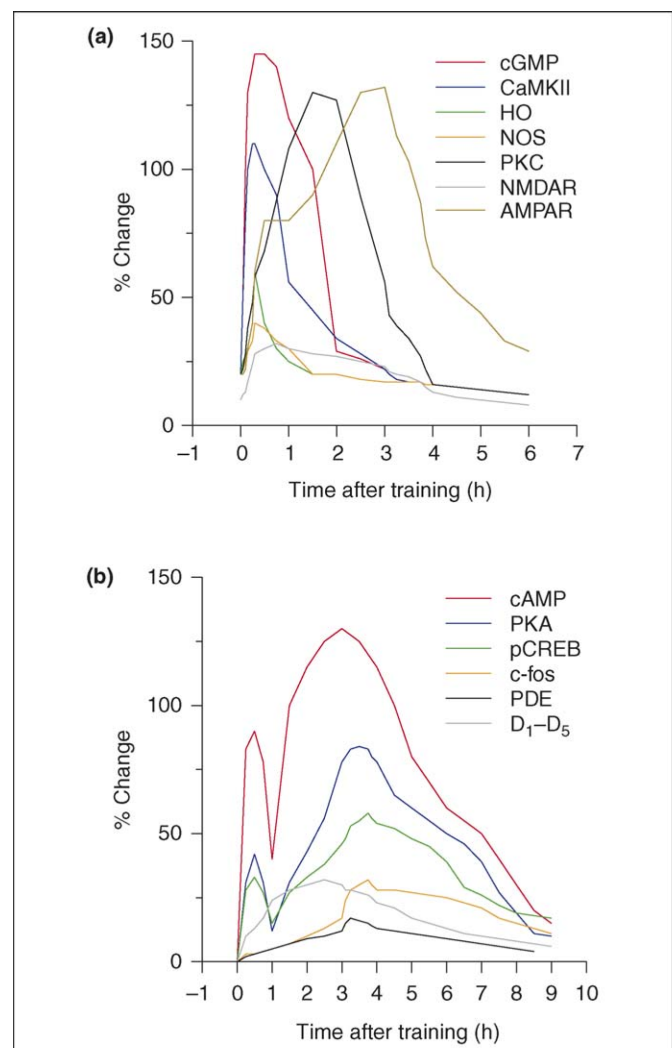

Figure 1. Sequence of molecular changes taking place in the hippocampus during memory consolidation. The values are best-fit curves; see the main text for references for the actual data. **(a)** Changes measured in the first few hours following training in the activity of cGMP, Ca^{2+}/calmodulin-dependent kinase II (CaMK II), haem oxygenase (HO), nitric oxide synthase (NOS) and protein kinase C, and in the binding of AMPA receptors (AMPAR) and NMDA receptors (NMDAR) to hippocampal membranes. **(b)** Changes seen over a longer period in the activity of cAMP, protein kinase A (PKA), phosphorylated cAMP-responsive-element-binding protein (pCREB), c-fos and phosphodiesterase (PDE), and in the binding of D_1–D_5 dopamine receptors to hippocampal membranes. ERK activity is not included here because it has been measured so far at only one interval (2 h from training) [73].

receptors and other receptors, and it might also participate in the phosphorylation of the transcription factor cAMP-responsive-element-binding protein (CREB) [37,44,47]. The need for molecular sequences of events in LTP and in memory formation, and the actual existence of those intertwined chains, has been commented upon many times [1,7,9,10,37,44]. The main biochemical findings concerning the role of hippocampus in consolidation of one-trial avoidance are summarized in Figure 1; the main pharmacological findings are surveyed in Table 1.

CA1 LTP uses most of these mechanisms in a similar sequence to the one we have just described for memory consolidation [1,44,47]. For example, LTP in CA1 requires activation of both the cAMP-dependent protein kinase (PKA) and the extracellular-signal-regulated kinase (ERK) pathways 2–4 h after induction [47–49]; memory consolidation in CA1 requires PKA twice, first immediately after training and then again 2–6 h later [9,50]. Inhibition of PKA in CA1 either shortly after training or 3–6 h later, but not at intermediate periods [50,51], cancels consolidation of one-trial avoidance. PKA is necessary in the hippocampus for the consolidation of various forms of learning [38], in the entorhinal cortex for inhibitory avoidance [52] and in the amygdala for at least some forms of conditioned fear [53]. The ERK pathway is necessary in CA1 for LTP [54–56] and for consolidation of inhibitory avoidance, conditioned fear and spatial learning [57–59], in the entorhinal cortex for one-trial avoidance [57], and in the amygdala for conditioned fear [16].

The PKA and ERK pathways mediate phosphorylation of CREB 2–6 h after both LTP induction and behavioral training [60–62]. CREB inactivation ~4 h post-training blocks memory storage of different tasks [63,64], and also LTP late maintenance (i.e. persistence beyond 2–4 h) [49,50]. The ERK pathway couples PKA to PKC in the regulation of CREB activation in CA1 [47]. The CREB phosphorylation associated with learning events might actually result from the novelty or stress inherent to the tasks [65,66].

Readers interested in the roles of other molecular processes in LTP and in memory storage in CA1 or elsewhere are referred to other sources (e.g. protein kinase G and retrograde messengers [67], phospholipases, phosphoinositol-3-kinase [68,69], adenylyl cyclase [12], JNK [70] and Src [71]). Operation of these other molecular pathways is linked to those already cited but they have been comparatively less studied, both in memory formation and in LTP.

Thus, there are many close similarities between the molecular basis of CA1 LTP and the role of CA1 in memory formation. The only noteworthy difference is that the activation of PKA and CREB, and accompanying gene expression and protein synthesis, of LTP take place once, at 3–6 h from induction, and those of consolidation take place twice, immediately after training and then again 2–6 h later [72]. This is probably because in LTP the hippocampus is studied in isolation, whereas in memory experiments it is studied *in situ,* exposed to a number of modulatory systems [14] (Table 1). This is in agreement

Table 1. Biochemical findings concerning the role of the CA1 region of the hippocampus in consolidation of one-trial avoidance[a,b]

Treatment	Time of infusion (min post-training)						Refs
	0	30	90	180	270	360	
Drugs affecting transmission by glutamate or GABA							
AP5 (−)	4	97	89	91	82	93	[14,80]
CNQX (−)	8	7	7	14	98	113	[13,30]
AP3 (−)	12	15	78	9	78	70	[13]
Muscimol (+)	0	109	103	78	92	104	[14]
Bicuculline (−)	180	–	180	95	78	103	[99]
Drugs affecting PKA activity							
Sp-cAMPs (+)	496	106	99	874	–	–	[51]
8-Br-cAMP (+)	88	–	93	373	–	338	[14]
KT5720 (−)	8	–	79	4	11	8	[14]
Rp-cAMPs (−)	13	82	89	8	–	–	[51]
Forskolin (+)	110	–	106	336	–	290	[14]
SKF38393 (+)	83	–	98	343	–	350	[14]
SCH23390 (−)	86	–	106	8	–	7	[14]
Noradrenaline (+)	390	–	87	460	–	422	[14]
Timolol (−)	108	–	79	3	–	5	[14]
8-OH-DPAT (−)	103	–	84	7	–	4	[14]
NAN-190 (+)	88	–	93	393	–	368	[14]
Drugs affecting other signaling pathways							
KN62 (−) [CaMKII]	22	47	54[c]	106	–	–	[109]
CGP41231 (−) [PKC]	5	15	62[c]	102	–	–	[9]
U0126 (−) [ERK1/2]	8	70	108	10	83	107	[14]

[a]Numbers indicate performance in a retention test by animals treated at various times after training with different drugs, as percentages relative to the performance of controls (mean latency of controls was 35–58 s depending on the experiment, with a maximum of 180 s). Doses can be found in the original papers.

[b](−) indicates inhibitors; (+) indicates stimulants. AP5, CNQX and AP3 are antagonists of NMDA, AMPA and metabotropic glutamate receptors, respectively. Muscimol and bicuculline are an agonist and antagonist of $GABA_A$ receptors, respectively. Sp-cAMPs and 8-Br-cAMP are PKA activators, whereas KT5720 and Rp-cAMPs inhibit this enzyme. Forskolin is an adenyl cyclase activator. SKF38393 and SCH23390 are an agonist and antagonist of dopamine D_1 receptors, respectively. Timolol is a β-adrenoceptor antagonist. 8-OH-DPAT and NAN-190 are an antagonist and agonist of $5HT_{1A}$ receptors, respectively. KN62, CGP41231 and U0126 inhibit CaMKII, PKC and MEK1/2 (the kinases that activate ERK1/2), respectively. Red and blue text respectively indicates decreases and increases that are significant to at least $P < 0.03$ in a non-parametric test. Dashes indicate that data have not been reported.

[c]120 instead of 90 min post-training.

Table 2. Biochemical findings concerning the role of the basolateral amygdala in consolidation of one-trial avoidance[a]

Treatment	Time of infusion (min post-training)						Refs
	0	30	90	180	270	360	
Drugs affecting transmission by glutamate or GABA							
AP5 (−)	20	128	93	91	83	112	[13]
CNQX (−)	7	–	17	8	–	86	[30]
AP3 (−)	8	6	76	108	116	78	[13]
Muscimol (+)	6	108	103	90	92	70	[14]
Picrotoxin (−)	180	–	–	–	–	–	[80]
Drugs affecting PKA activity							
8 Br cAMP (+)	107	–	–	103	–	104	[14]
KT5720 (−)	95	–	–	83	–	11	[14]
Forskolin (+)	110	–	–	80	–	91	[14]
SKF38393 (+)	84	–	–	93	–	100	[14]
SCH23390 (−)	119	–	–	99	–	96	[14]
Noradrenaline (+)	332	–	–	81	–	98	[14]
Timolol (−)	90	–	–	88	–	94	[14]
8-OH-DPAT (−)	101	–	–	89	–	95	[14]
NAN-190 (+)	97	–	–	93	–	101	[14]
Drugs affecting other signaling pathways							
KN62 (−) [CaMKII]	97	–	–	–	106	–	[109]
Gö7874 (−) [PKC generic]	7	4	77	57	60	87	[110]
Gö6976 (−) [PKC α/β]	11	6	80	60	110	88	[105]
U0126 (−) [ERK1/2]	18	10	9	10	112	107	[14]

[a]Details are as for Table 1, except that the mean latency of controls was 36–55 s depending on the experiment, with a maximum of 180 s. As before, (−) indicates inhibitors and (+) indicates stimulants, red (decrease) and blue (increase) figures are in all cases significant to at least $P < 0.03$ in a non-parametric test, and dashes indicate that data have not been reported. Picrotoxin is an antagonist of $GABA_A$ receptors. Gö7874 is total PKC inhibitor and Gö6976 is specific for the PKC α/β isoforms.

with findings from Matthies and co-workers [73], who 25 years ago showed similar post-training dual peaks of dopamine-mediated modulation and RNA and protein synthesis in the hippocampus.

Another, often overlooked, major coincidence between hippocampal memory and LTP mechanisms is the causal relationship between the early activation of NMDA receptors and the subsequent changes in PKA and ERK1/2 activity in one-trial memory formation [74] and in hippocampal LTP [75,76].

In all cases, studies of the molecular basis of memory consolidation (or of LTP formation) have been corroborated by studies in knockout or transgenic mice lacking or underexpressing a specific receptor or protein [60,62,77–82]. But it is not possible to determine timing of the onset and termination of a given molecular process with such animal models, and timing is at the essence of LTP and consolidation [37,44].

Main events in memory formation of one-trial learning in the basolateral amygdala, entorhinal cortex and posterior parietal cortex

Tables 2, 3 and 4 summarize the main published findings on memory consolidation in the basolateral amygdala,

Table 3. Biochemical findings concerning the role of the entorhinal cortex in consolidation of one-trial avoidance[a]

Treatment	Time of infusion (min post-training)						Refs
	0	30	90	180	270	360	
Drugs affecting transmission by glutamate or GABA							
AP5 (−)	120	19	15	21	103	118	[14]
CNQX (−)	106	115	101	92	93	111	[30]
AP3 (−)	11	8	7	66	108	103	[13]
Muscimol (+)	104	11	16	19	95	94	[14]
Bicuculline (−)	300	–	96	350	104	83	[99]
Drugs affecting PKA activity							
8 Br cAMP (+)	375	–	–	370	–	372	[14]
KT5720 (−)	7	–	–	11	–	7	[14]
Forskolin (+)	375	–	–	370	–	268	[14]
SKF38393 (+)	288	–	–	370	–	372	[14]
SCH23390 (−)	8	–	–	6	–	6	[14]
Noradrenaline (+)	375	–	–	370	–	372	[14]
Timolol (−)	8	–	–	8	–	9	[14]
8-OH-DPAT (−)	8	–	–	8	–	10	[14]
NAN-190 (+)	97	–	–	108	–	107	[14]
Drugs affecting other signaling pathways							
Gö7874 (−) [PKC generic]	15	–	–	116	–	–	[9]
U0126 (−) [ERK1/2]	10	88	84	8	107	6	[13]

[a]Details are as for Table 1, except that the mean latency of controls was 38–58 s depending on the experiment, with a maximum of 180 s. As before, (−) indicates inhibitors and (+) indicates stimulants, red (decrease) and blue (increase) figures are in all cases significant to at least $P < 0.03$ in a non-parametric test, and dashes indicate that data have not been reported.

Table 4. Biochemical findings concerning the role of the posterior parietal cortex in consolidation of one-trial avoidance[a]

Treatment	Time of infusion (min post-training)						Refs
	0	30	90	180	270	360	
Drugs affecting transmission by glutamate or GABA							
AP5 (−)	81	116	6	19	114	96	[14]
CNQX (−)	108	87	92	62	66	60	[30]
AP3 (−)	122	115	78	76	77	78	[13]
Muscimol (+)	6	108	103	90	92	70	[14]
Bicuculline (−)	400	–	92	360	103	77	[99]
Drugs affecting PKA activity							
KT5720 (−)	18	–	–	14	–	8	[14]
Forskolin (+)	110	–	–	340	–	350	[14]
SKF38393 (+)	84	–	–	76	–	108	[14]
SCH23390 (−)	89	–	–	10	–	8	[14]
Noradrenaline (+)	101	–	–	355	–	350	[14]
Timolol (−)	90	–	–	6	–	6	[14]
8-OH-DPAT (−)	105	–	–	7	–	7	[14]
NAN-190 (+)	94	–	–	90	–	111	[14]
Drugs affecting other signaling pathways							
CGP41231 (−) [PKC]	5	35	–	19	107	–	[9]
U0126 (−) [ERK1/2]	10	88	84	8	107	6	[14]

[a]Details are as for Table 1, except that here mean latency of controls was 34–53 s depending on the experiment, with a maximum of 180 s. As before, (−) indicates inhibitors and (+) indicates stimulants, red (decrease) and blue (increase) figures are in all cases significant to at least $P < 0.03$ in a non-parametric test, and dashes indicate that data have not been reported.

entorhinal cortex and posterior parietal cortex, respectively. There have been a few scattered findings on the posterior parietal cortex (a prolonged amnesic effect of the ERK1/2 inhibitor U0126 and of the GABA receptor agonist muscimol when given up to 3 h post-training [14]). Findings in other structures (e.g. the insular lobe and prefrontal areas) have been less consistent or fragmentary (e.g. a single dose and/or time of injection) and will not be included in this account.

As can be seen, the pattern of entry into action of each molecular process varies with the structure. For example, if one follows sensitivity to the amnesic effect of the NMDA receptor antagonist D(−)-2-amino-5-phosphonopentanoic acid (AP5) [14], it is possible to conclude that NMDA-receptors are needed in all the structures but at different times: immediately post-training in CA1 (Table 1) or the basolateral amygdala (Table 2), but 30 min later in the entorhinal cortex (Table 3) and 90 min later in parietal cortex (Table 4). In the entorhinal and parietal cortex, susceptibility to AP5 also lasts much longer than in the hippocampus and amygdala. It is often taken for granted that memory consolidation begins with an AP5-sensitive process [1,9,10,13,14,34]. Sensitivity to NMDA receptor blockers is usually accompanied by enhanced susceptibility to the inhibitory effect of muscimol and to the facilitatory effect of $GABA_A$ receptor blockers [83]. Thus, the process of memory consolidation appears to be accompanied and followed by AMPA-receptor-dependent processes [9,10,30] in all the structures studied except the entorhinal cortex [13] (Table 3).

In the CA1 region, the effects of AP5, muscimol and the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) are accompanied and/or followed by changes in the activity of CaMKII, PKC, ERK1/2 and PKA, and/or in susceptibility to their inhibitors (Table 1). This is not always the case in the other structures: the amygdala features ERK-dependent events early on, which last for several hours, but no PKA-related events [14]. (However, it does feature PKA-related events in other aversive tasks [53].) The events related to PKC have different times of initiation and different duration: they occur early in CA1 (Table 1), the amygdala (Table 2) and the parietal cortex (Table 4), but 4–6 h later in the entorhinal region (Table 3).

Therefore, it is difficult to view the changes seen in the amygdala, parietal cortex and entorhinal region as indicative or suggestive of LTP [37,44]; they appear, rather, to pertain to other forms of plasticity that share some steps with LTP but not their sequence.

It is apparent from Tables 1, 3 and 4 that PKA-related mechanisms are out of synchrony with the timing of processes involving glutamate receptor processes [9–14]. As already mentioned, PKA-related mechanisms are required in CA1 twice, at time 0 and again at 3–6 h from training; in the entorhinal cortex they are important at all times between 0 h and 6 h post-training; in the parietal cortex they participate only 3–6 h post-training; and in the amygdala they seem not to participate at all in this task [10,12].

The ERK1/2 pathway is necessary at widely different times in the different structures. In CA1 (Table 1) and the parietal cortex (Table 4), ERKs are required immediately after training and then again 3 h later; they seem to be required during the first 6 h after training in the entorhinal cortex (Table 3), and not at all in the amygdala [9,14] (Table 2).

The role of CaMKII was investigated only in the hippocampus (Table 1) and amygdala (Table 2). This enzyme is crucial for the phosphorylation and upregulation of AMPA receptor function in CA1 after both LTP induction and inhibitory avoidance training [38–42]. In addition, CaMKII is also involved in the phosphorylation of numerous postsynaptic density proteins, including PSD-95, α- tubulin, β-tubulin, dynamin, α-internexin and cAMP phosphodiesterase [9,10].

The molecular processes of memory formation are sensitive to modulation by synapses that use dopamine D_1

receptors, β-adrenoceptors and 5-HT_{1A} receptors in the hippocampus and entorhinal and parietal cortex [10,12,50] (Tables 1, 3 and 4) and, as shown elsewhere, also by synapses that use muscarinic and nicotinic ACh receptors [9,17]. Activity of all these synapses is known to correlate with brain processes involved in the perception of and the reaction to emotion-related, mood-related and arousal-related processes. The monoamines dopamine, noradrenaline, 5-hydroytryptamine (5-HT) and ACh all affect cAMP synthesis and thus regulate PKA [9,10,14].

The timing of the intervention of the various molecular processes revealed by pharmacological studies has been corroborated by biochemical analyses. Figure 1 illustrates best-fit drawings of data published elsewhere on receptor binding, enzyme activity or protein synthesis in CA1 at different times after training [39,40,45,46,50–53,74]. As can be seen, these features peak precisely at the times when they are most sensitive to the respective inhibitors: CaMKII activity at 0–1 h from training, PKA activity and CREB levels immediately after training and then again at 3–6 h hours after training, ERK activity 1–2 h after training [74], and PKC activity ~30 min after training [43–45]. Importantly, the post-training peaks of c-fos, PKA, CaMKII and ERK1/2 activity in CA1 depend on previous stimulation of NMDA receptors: if NMDA is administered to CA1 at the time of training, the peaks are not seen in the hippocampus, either in one-trial learning [40–73] or in LTP [74,75]. Figure 1 also includes data on nitric oxide synthase, haem oxygenase, cGMP, cAMP, cAMP-phosphodiesterase and c-fos [67].

The structures studied in Tables 1–4 are all interconnected by afferent and efferent fibers via the entorhinal cortex [26,27], so they probably operate in orchestrated fashion in memory consolidation [1–6,8–10,22,49,50]. That many of the disruptive agents used in the various structures can block memory completely indicates that most of those mechanisms are necessary for memory formation.

What forms of plasticity are involved in each structure?

Clearly, in CA1 the form of plasticity involved in memory consolidation is one closely similar to LTP, if not actual LTP [1–10]. In the other structures the sequences of molecular processes are different from those described for LTP. However, the receptors involved (particularly the NMDA receptor) [9–11,14,34,36,83] and the function of the enzymes involved (particularly their relationship to receptor activation, CREB phosphorylation, gene expression, protein synthesis and the build-up of extra cellular connectivity) [19] points to specific influences in plastic events. The molecular processes studied have all been ascribed a role in plasticity [76,83–85].

It is possible that each brain structure processes a different informational (e.g. cognitive versus emotional) aspect of each task [86–89], but this remains to be proven. Current evidence is insufficient for this postulation.

Why are emotionally-rich memories usually better consolidated?

The post-training hippocampal PKA activation and CREB phosphorylation, and memory consolidation itself, are highly sensitive to dopamine receptor agonists and to antagonists acting on D_1 receptors, β-adrenoceptors and 5HT_{1A} receptors [50] (Tables 1, 3 and 4). The pathways ending on dopamine D_1 receptors and β-adrenoceptors in the hippocampus and neocortex are well known to mediate alertness, emotion and anxiety levels. D_1 receptors and β-adrenoceptors enhance, and 5HT_{1A} receptors depress, adenylyl cyclase activity, and therefore cAMP production and indirectly PKA activity [9–13]. Thus, these pathways can regulate the PKA-dependent CREB phosphorylation processes that underlie memory consolidation [12,50,61].

The data in Table 1 strongly implicate the enhancement of events mediated by cAMP, PKA and CREB in the strong fixation of emotionally-laden memories [9,10] – memories that have been called flashbulb memories and are usually remembered with great precision [87–89].

An additional factor in the fixation of highly emotional memories could certainly be the enhanced activity of the ERK signaling pathway [54,66] that results from the aversive component of the one-trial avoidance task [66] (and probably also from other task components [53]). The post-training role of ERKs in consolidation in the basolateral amygdala is certainly longer than in any other brain structure studied so far (Table 2) [14].

A third and possibly major reason why consolidation of emotional memories is usually better and more resistant than that of non-emotional memories is of course the activation of the basolateral amygdala itself when these memories are acquired [10,18,88,89]. But clearly the basolateral amygdala is not the only regulator of emotional memory formation or retrieval. The monoamine receptor–PKA–CREB systems [50,61] and ERK must have a role that is at least as important and, if anything, far more direct.

Endogenous state dependency revisited

Tables 1–4 show that memory consolidation is accompanied and regulated by different neuromodulatory and molecular ‘states’. So is retrieval [89]. Memories, particularly those of an emotional type, have been suggested to rely on an endogenous state-dependent process [90–93].

Both consolidation and retrieval of one-trial avoidance require PKA and ERK activity in the hippocampus, the entorhinal, parietal and cingulate cortex and the basolateral amygdala, and both are modulated by D_1 receptors, β-adrenoceptors, 5HT_{1A} receptors and muscarinic ACh receptors in all these structures [89]. In addition, peripheral hormones and brain opioids [92–95] are as important in modulating retrieval as they are in modulating consolidation, and might be involved in endogenous state dependency. Further work on this is desirable [93]. For additional information on this topic, see Refs [93–95].

A note on the parallel processing of immediate, short-term and long-term memory

STM is now known to last ~3–6 h and is processed in parallel to the consolidation of LTM [21,22]. Before that, and as a precondition for both STM and LTM formation, working memory (WM) handles the information that is to be saved while it is being acquired and/or for a few seconds afterwards [9–11]. The mechanisms of WM and STM are in general not directly related to those of LTM formation, and

Table 5. Effect on working memory and short-term memory of drugs given into the CA1 region of hippocampus, entorhinal cortex or parietal cortex[a,b]

Treatment	Region						Refs
	CA1		Entorhinal cortex		Parietal cortex		
	WM	STM	WM	STM	WM	STM	
AP5 (−)	100	14	100	98	155	95	[11,90]
CNQX (−)	14	15	17	20	18	16	[11,90]
MCGP (−)	100	–	–	102	–	–	[11]
Muscimol (+)	11	11	13	22	4	8	[11,90]
KT5720 (−)	–	18	–	30	–	–	[90]
PD098059 (−)	–	13	–	209	–	–	[11]
SKF38393 (+)	–	20	–	16	–	–	[11]
SCH23390 (−)	5	208	100	–	7	106	[11,90]
NE (+)	–	96	–	211	–	–	[11,90]
Timolol (−)	–	85	–	16	–	–	[11,90]
8-OH-DPAT (−)	–	6	–	290	–	–	[11]
NAN-190 (+)	–	82	–	17	–	–	[11]
Scopolamine (−)	14	92	10	101	11	11	[11,90]

[a]Effect of drugs given into the CA1 region of hippocampus, the entorhinal cortex or the parietal cortex on working memory (WM) measured 3 s after training and on short-term memory (STM) measured 1.5 h after training. The drugs were given 5 min prior to training in the former case and immediately post-training in the latter. Data are expressed as percentage of retention-test performance relative to controls in the animals tested for working memory (mean latency of controls, 100–180 s) and in short-term memory (mean control latency, 41–46 s).

[b](−) indicates inhibitors and (+) indicates stimulants. (S)-α-methyl-4-carboxyphenylglycine (MCGP) is an antagonist of metabotropic glutamate receptors, PD098059 is an antagonist of ERK, and scopolamine is an agonist of muscarinic ACh receptors (for other activities, see Table 1). Doses can be found in the original papers. Red (decrease) and blue (increase) figures are in all cases significant to at least $P < 0.03$ in a non-parametric test, and dashes indicate that data have not been reported. Note than in most cases the results are different qualitatively from those obtained for LTM in Tables 1–4.

the interested reader is referred to Ref. [11] for a recent review of this topic.

Several of the treatments shown in Tables 1–4 have been studied for their effect on WM and STM. The findings are summarized in Table 5. In other words, Table 5 shows effects on memory types measured at 0 min or 90 min following training of treatments that, when given at those times, can profoundly affect LTM measured one day later. As can be seen, there are many differences between the drug effects on WM and those on LTM. None of the treatments shown in Table 5 was found to affect either WM or STM when given into the amygdala [22].

Comparison of the findings of Table 5 with those of Tables 1–4 illustrates the separation of WM, STM and LTM from a mechanistic point of view [9,10,22,70,71]. It is likely that the three forms of memory are processed by the same cells and synapses in the hippocampus, amygdala and parietal cortex because it is hard to believe that the same set of stimuli, associations and responses would be processed by different subsets of neurons at the same time in several brain structures. The type of storage system (WM, STM or LTM) that will handle each given set of stimuli, associations and responses is probably decided by the influences of the signaling pathways that are simultaneously triggered into action, in parallel, at the time of training on different substrates [11,21,22]. This is the case for STM and LTM: STM requires PKA during the first 90 min post-training, whereas LTM requires it at 0 min and again at 170 min or more, but not at the intermediate periods [51]. This strongly suggests mediation by different substrates; for example, CREB is a PKA substrate clearly involved in LTM [50] but not in STM [72].

A caveat

The list of brain areas that participate in memory consolidation is certainly longer than the one we have discussed in this review. If CA1 and the entorhinal cortex participate, then surely the dentate gyrus and CA3 must be involved [33]. Recent evidence supports this [94]. The same stands for other molecules not specifically discussed here. For example, recent data point to a key role for the ubiquitin–proteasome system [96] and brain-derived neurotrophic factor (BDNF) [97–99] in STM and LTM formation. Further research will surely add to the information shown in Tables 1–4.

Can a neural network be proposed?

The sequence of events in CA1 LTP has been worked out by several authors [1,3–6]. However, beyond the early NMDA receptor activation, and the subsequent increase in $[Ca^{2+}]_i$, activation of CaMKII and enhancement of AMPA receptor, PKC and PKA activity, things become blurred and it is difficult to be precise, especially about timing [44]. There could also be alternative connections between metabolic routes, particularly those involving signaling pathways and gene activation [7]. Indeed, LTP in the dentate gyrus, CA3 and other neural structures uses many such 'alternative' routes to those of CA1 [1–8]. However, the key factor in most accounts still is timing [37,44]: activation of a given enzyme must precede phosphorylation and activation of its substrate(s), the action of signaling pathways must precede gene activation, and so on. The same might be said of metabolic sequences underlying memory formation in CA1 [9,10] (Table 1) or elsewhere (Tables 2–4). Therefore, from a cellular point of view, at this stage of knowledge in the field it seems presumptuous to propose a reasonably heuristic schema of a blueprint.

The anatomical connections between the hippocampus, amygdala, entorhinal cortex and parietal cortex have been relatively well studied [27] and some simple diagrams can be envisaged at the systems level. Where does the entire memory consolidation process begin? Most evidence points to the hippocampus [1–4,7–11,21–24,39,63,73]. In some previous articles, based on the postulations of Bliss and Collingridge [1] and others [2–7], we have suggested that one way to answer this question might be to discover which

regions in the brain first become susceptible to AP5. This susceptibility usually but not always begins at the same time as susceptibility to muscimol [14,100].

Stimulation of CA1 sets into reverberation the CA1–subiculum–entorhinal–dentate–CA3–CA1 circuit, at a fast rate [101]. From the systems point of view, information leading to memory consolidation should flow from CA1 through the subiculum and then the entorhinal cortex to the rest of the cortex and the basolateral amygdala [9,27,87,88], which in turn should project back to the entorhinal cortex and the hippocampal dentate–CA3–CA1 system [27,90]. But so far there have been no systematic pharmacological studies that begin with the dentate gyrus or CA3; such studies have been conducted only in the entorhinal cortex (Table 3). So, here again, attempts to propose a clear-cut blueprint at the circuits level would currently be too speculative.

Of course many other pathways besides those mentioned are possible [31,102], and surely in different forms of memory, with different sensory or motor components and cognitive content, the variety of pathways and perhaps molecular mechanisms that participate is likely to be larger than we currently realize. No doubt, reverberation in CA1–entorhinal–dentate–CA3–CA1 circuits [101] should occur not only horizontally but also longitudinally, with the circle widening as the distance from the initial point of activation increases. In addition, it must not be forgotten that, as is true in the entorhinal cortex and the CA1, all other connections among the hippocampus, amygdala and neocortex are bidirectional [9,27,87,88,101].

There is no indication that there are single mechanisms for synaptic plasticity, LTP or memory consolidation. It would make little adaptive sense if it were so. In all likelihood there are many interconnected, and perhaps replaceable, systems that can produce satisfactory forms of plasticity leading to similar responses. Further, the participation of these areas might change, particularly with repetition. If animals are exposed to a step-down avoidance task for a second time [83], the striatum enters into play on the second session instead of the hippocampus. This should require the installment a completely new set of anatomical connections in order to relearn essentially the same response to the same constellation of stimuli, only to a larger extent. So to postulate fixed circuits for a given set of stimuli (and learned responses) sounds too rigid. Studies on the recovery of people bearing large brain lesions [103,104] should make us all less phrenologically minded (i.e. believing that one behavior equals one circuit) and more 'plastic' [1,9,83]. Memories do change, and the brain circuits used by experts have long been known not to be the same ones that they used when they were apprentices.

One last, and hopefully haunting, question. Memories can be 'infected' by false information at any time [105,106], but particularly in the first few hours after acquisition [107,108], precisely when they are being consolidated and when STM is active [21,22]. Are any of the molecular mechanisms commented upon in this article or elsewhere [9,10] particularly involved with the introduction of false data in memories? This is a point that should, indeed, be investigated.

Concluding remarks

Different chains of molecular events involving glutamate receptors, CaMKII, PKA, PKC and ERK1/2 are necessary for LTM formation in the CA1 region of the hippocampus, basolateral amygdala, entorhinal cortex, parietal cortex and cingulate cortex. The time course of the events in CA1 is similar but not identical to that which underlies LTP in this area. The timings of the molecular events in the other structures differ from each other and from those in CA1. Several of the biochemical events analyzed point to the reasons why emotionally-laden memories are usually better consolidated than neutral memories; particularly relevant seems to be the regulation of the crucial PKA–CREB step of memory formation by neurotransmitters related to mood and emotion.

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References

1 Bliss, T.V. and Collingridge, G.L. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361, 31–39
2 Riedel, G. *et al.* (2003) Glutamate receptor function in learning and memory. *Behav. Brain Res.* 140, 1–47
3 Malenka, R.C. and Nicoll, R.A. (1999) Long-term potentiation – a decade of progress? *Science* 285, 1870–1874
4 Kandel, E.R. and Squire, L.R. (2000) Neuroscience: breaking down scientific barriers to the study of brain and mind. *Science* 290, 1113–1120
5 Martin, S.J. *et al.* (2000) Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu. Rev. Neurosci.* 23, 649–711
6 Malenka, R.C. (2003) The long-term potential of LTP. *Nat. Rev. Neurosci.* 4, 923–926
7 Ahmed, T. and Frey, J.U. (2005) Plasticity-specific phosphorylation of CaMKII, MAP-kinases and CREB during late-LTP in rat hippocampal slices *in vitro*. *Neuropharmacology* 49, 477–492
8 Morris, R.G. *et al.* (2003) Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 773–786
9 Izquierdo, I. and Medina, J.H. (1997) Memory formation: the sequence of biochemical events in the hippocampus and its connection to activity in other brain structures. *Neurobiol. Learn. Mem.* 68, 285–316
10 Izquierdo, I. and McGaugh, J.L. (2000) Behavioural pharmacology and its contribution to the molecular basis of memory consolidation. *Behav. Pharmacol.* 11, 517–534
11 Izquierdo, L.A. *et al.* (2002) Molecular pharmacological dissection of short- and long-term memory. *Cell. Mol. Neurobiol.* 22, 269–287
12 Ardenghi, P. *et al.* (1997) Late and prolonged post-training memory modulation in entorhinal and parietal cortex by drugs acting on the cAMP/protein kinase A signalling pathway. *Behav. Pharmacol.* 8, 745–751
13 Bonini, J.S. *et al.* (2003) AMPA/kainate and group-I metabotropic receptor antagonists infused into different brain areas impair memory formation of inhibitory avoidance in rats. *Behav. Pharmacol.* 14, 161–166
14 Rossato, J.I. *et al.* (2004) Retrograde amnesia induced by drugs acting on different molecular systems depends on how long after training these drugs are infused in selected brain areas. *Behav. Neurosci.* 118, 563–568
15 Sacchetti, B. *et al.* (1999) Auditory thalamus, dorsal hippocampus, basolateral amygdala, and perirhinal cortex role in the consolidation of conditioned freezing to context and to acoustic conditioned stimulus in the rat. *J. Neurosci.* 19, 9570–9578
16 Schafe, G.E. *et al.* (2001) Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *Trends Neurosci.* 24, 540–546
17 Brioni, J.D. (1993) Role of GABA during the multiple consolidation of memory. *Drug Dev. Res.* 28, 3–27

18 McGaugh, J.L. (2000) Memory – a century of consolidation. *Science* 287, 248–251

19 Rose, S.P.R. (1995) Time-dependent biochemical and cellular processes in memory formation. In *Plasticity in the Central Nervous System* (McGaugh, J.L. *et al.*, eds), pp. 171–184, Lawrence Erlbaum

20 Ng, K.T. *et al.* (1997) Complex roles of glutamate in the Gibbs–Ng model of one-trial aversive learning in the new-born chick. *Neurosci. Biobehav. Rev.* 21, 45–54

21 Izquierdo, I. *et al.* (1998) Mechanisms for memory types differ. *Nature* 393, 635–636

22 Izquierdo, L.A. *et al.* (2000) Short- and long-term memory are differentially affected by metabolic inhibitors given into hippocampus and entorhinal cortex. *Neurobiol. Learn. Mem.* 73, 141–149

23 Dudai, Y. and Eisenberg, M. (2004) Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* 44, 93–102

24 Squire, L.R. (1987) *Memory and Brain.* Oxford University Press

25 Dudai, Y. (2004) The neurobiology of consolidations, or, how stable is the engram? *Annu Rev. Psychol.* 55, 51–86

26 Suzuki, W.A. and Amaral, D.G. (2004) Functional neuroanatomy of the medial temporal lobe memory system. *Cortex* 40, 220–222

27 Hyman, B.T. *et al.* (1990) Memory-related neural systems in Alzheimer's disease: an anatomic study. *Neurology* 40, 1721–1730

28 Bontempi, B. *et al.* (1999) Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature* 400, 671–675

29 Morris, R.G. *et al.* (1986) Selective impairment of learning and blockade of long-term potentiation by an *N*-methyl-D-aspartate receptor antagonist, AP5. *Nature* 319, 774–776

30 Jerusalinsky, D. *et al.* (1992) Amnesia by post-training infusion of glutamate receptor antagonists into the amygdala, hippocampus and entorhinal cortex. *Behav. Neural Biol.* 58, 76–80

31 Lorenzini, C.A. *et al.* (1996) Role of dorsal hippocampus in acquisition, consolidation and retrieval of rat's passive avoidance response: a tetrodotoxin functional inactivation study. *Brain Res.* 730, 32–39

32 Riedel, G. *et al.* (1999) Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nat. Neurosci.* 2, 898–905

33 Green, J.D. (1964) The hippocampus. *Physiol. Rev.* 44, 561–608

34 Kim, M. and McGaugh, J.L. (1992) Effects of intra-amygdala injections of NMDA receptor antagonists on acquisition and retention of inhibitory avoidance. *Brain Res.* 585, 35–48

35 McClelland, J.L. *et al.* (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457

36 Bianchin, M. *et al.* (1994) Memory of inhibitory avoidance in the rat is regulated by glutamate metabotropic receptors in the hippocampus. *Behav. Pharmacol.* 5, 356–359

37 Carew, T.J. and Sutton, M.A. (2001) Molecular stepping stones in memory consolidation. *Nat. Neurosci.* 4, 769–771

38 Barria, A. *et al.* (1997) Regulatory phosphorylation of AMPA-type glutamate receptors by CaM-KII during long-term potentiation. *Science* 276, 2042–2045

39 Cammarota, M. *et al.* (1998) Learning-specific, time-dependent increases in hippocampal Ca^{2+}/calmodulin-dependent protein kinase II activity and AMPA GluR1 subunit immunoreactivity. *Eur. J. Neurosci.* 10, 2669–2676

40 Bevilaqua, L.R.M. *et al.* (2005) Memory consolidation induces *N*-methyl-D-aspartic acid-receptor- and Ca^{2+}/calmodulin-dependent protein kinase II-dependent modifications in α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor properties. *Neuroscience* 136, 397–403

41 Cammarota, M. *et al.* (1995) Inhibitory avoidance training induces rapid and selective changes in ^{3}[H]AMPA receptor binding in the rat hippocampal formation. *Neurobiol. Learn. Mem.* 64, 257–264

42 Cammarota, M. *et al.* (1996) Reversible changes in hippocampal ^{3}[H]-AMPA binding following inhibitory avoidance training in the rat. *Neurobiol. Learn. Mem.* 66, 85–88

43 Colley, P.A. and Routtenberg, A. (1993) Long-term potentiation as synaptic dialogue. *Brain Res. Rev.* 18, 115–122

44 Routtenberg, A. (2000) It's about time. In *Memory Consolidation* (Gold, P.E. and Greenough, W.T., eds), pp. 17–34, American Psychological Association

45 Paratcha, G. *et al.* (2000) Involvement of hippocampal PKCβI isoform in the early phase of memory formation of an inhibitory avoidance learning. *Brain Res.* 855, 199–205

46 Cammarota, M. *et al.* (1997) B50/GAP43 phosphorylation and PKC activity are increased in rat hippocampal synaptosomal membranes after an inhibitory avoidance learning. *Neurochem. Res.* 22, 499–505

47 Roberson, E.D. *et al.* (1999) The mitogen-activated protein kinase cascade couples PKA and PKC to cAMP response element binding protein phosphorylation in area CA1 of hippocampus. *J. Neurosci.* 19, 4337–4348

48 Huang, Y.Y. *et al.* (1994) cAMP contributes to mossy fiber LTP by initiating both a covalently mediated early phase and macromolecular synthesis-dependent late phase. *Cell* 79, 69–79

49 Huang, Y.Y. and Kandel, E.R. (1996) Modulation of both the early and the late phase of mossy fiber LTP by the activation of β-adrenergic receptors. *Neuron* 16, 611–617

50 Bernabeu, R. *et al.* (1997) Involvement of hippocampal D1/D5 receptor-cAMP signaling pathways in late memory consolidation. *Proc. Natl. Acad. Sci. U. S. A.* 94, 7041–7046

51 Vianna, M.R. and Izquierdo, I. (2004) Protein kinase A. In *Memories are Made of these: From Messengers to Molecules* (Riedel, G. and Platt, B., eds), pp. 369–382, Kluwer Academic/ Plenum Publishers

52 Pereira, P. *et al.* (2001) Training in the step-down inhibitory avoidance task time-dependently increases cAMP-dependent protein kinase activity in the entorhinal cortex. *Behav. Pharmacol.* 12, 217–220

53 Schafe, G.E. and LeDoux, J.E. (2000) Memory consolidation of auditory pavlovian fear conditioning requires protein synthesis and protein kinase A in the amygdala. *J. Neurosci.* 20, RC96

54 Sweatt, J.D. (2004) Mitogen-activated protein kinases in synaptic plasticity and memory. *Curr. Opin. Neurobiol.* 14, 311–317

55 English, J.D. and Sweatt, J.D. (1997) A requirement for the mitogen-activated protein kinase cascade in hippocampal long term potentiation. *J. Biol. Chem.* 272, 19103–19106

56 Kanterewicz, B.I. *et al.* (2000) The extracellular signal-regulated kinase cascade is required for NMDA-R-independent LTP in area CA1 but not area CA3 of the hippocampus. *J. Neurosci.* 20, 3057–3066

57 Walz, R. *et al.* (1999) Effects of post-training infusions of a mitogen-activated protein kinase kinase inhibitor into the hippocampus or entorhinal cortex on short- and long-term retention of inhibitory avoidance. *Behav. Pharmacol.* 10, 723–730

58 Atkins, C.M. *et al.* (1998) The MAPK cascade is required for mammalian associative learning. *Nat. Neurosci.* 1, 602–609

59 Schafe, G.E. *et al.* (1999) Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase. *Learn. Mem.* 6, 97–110

60 Silva, A.J. *et al.* (1998) CREB and memory. *Annu. Rev. Neurosci.* 21, 127–148

61 Taubenfeld, S.M. *et al.* (1999) A molecular correlate of memory and amnesia in the hippocampus. *Nat. Neurosci.* 2, 309–310

62 Kida, S. *et al.* (2002) CREB required for the stability of new and reactivated fear memories. *Nat. Neurosci.* 5, 348–355

63 Guzowski, J.F. and McGaugh, J.L. (1997) Antisense oligodeoxynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proc. Natl. Acad. Sci. U. S. A.* 94, 2693–2698

64 Pittenger, C. *et al.* (2002) Reversible inhibition of CREB/ATF transcription factors in region CA1 of the dorsal hippocampus disrupts hippocampus-dependent spatial memory. *Neuron* 34, 447–462

65 Winograd, M. and Viola, H. (2004) Detection of novelty, but not memory of spatial habituation, is associated with an increase in phosphorylated cAMP response element-binding protein levels in the hippocampus. *Hippocampus* 14, 117–123

66 Alonso, M. *et al.* (2002) Aversive experiences are associated with a rapid and transient activation of ERKs in the rat hippocampus. *Neurobiol. Learn. Mem.* 77, 119–124

67 Medina, J.H. and Izquierdo, I. (1995) Retrograde messengers, long-term potentiation, and memory processes. *Brain Res. Rev.* 21, 185–194

68 Barros, D.M. *et al.* (2001) LY294002, an inhibitor of phosphoinositide 3-kinase given into rat hippocampus impairs acquisition, consolidation and retrieval of memory for one-trial inhibitory avoidance. *Behav. Pharmacol.* 12, 629–634
69 Lubin, F.D. *et al.* (2005) Kainate mediates nuclear factor-κB activation in hippocampus via phosphatidylinositol-3 kinase and extracellular signal-regulated protein kinase. *Neuroscience* 133, 969–981
70 Bevilaqua, L.R. *et al.* (2003) Inhibition of hippocampal Jun N-terminal kinase enhances short-term memory but blocks long-term memory formation and retrieval of an inhibitory avoidance task. *Eur. J. Neurosci.* 17, 897–902
71 Bevilaqua, L.R. *et al.* (2003) Src kinase activity is required for avoidance memory formation and recall. *Behav. Pharmacol.* 14, 649–652
72 Igaz, L.M. *et al.* (2002) Two time periods of hippocampal RNA synthesis are required for memory consolidation of fear-motivated learning. *J. Neurosci.* 22, 6781–6789
73 Matthies, H. (1982) Plasticity in the nervous system – an approach to memory research. In *Neural Plasticity and Memory Formation* (Ajmone-Marsan, C. and Matthies, H., eds), pp. 1–16, Raven Press
74 Cammarota, M. *et al.* (2000) Learning-associated activation of nuclear MAPK, CREB and Elk-1, along with Fos production, in the rat hippocampus after a one-trial avoidance learning: abolition by NMDA-R blockade. *Mol. Brain Res.* 76, 36–46
75 English, J.D. and Sweatt, J.D. (1996) Activation of p42 mitogen activated protein kinase in hippocampal long-term potentiation. *J. Biol. Chem.* 271, 24329–24332
76 Roberson, E.D. and Sweatt, J.D. (1996) Transient activation of cyclic AMP-dependent protein kinase during hippocampal long-term potentiation. *J. Biol. Chem.* 271, 30436–30441
77 Mayford, M. *et al.* (1996) Control of memory formation through regulated expression of a CaMKII transgene. *Science* 274, 1678–1686
78 Huang, Y.Y. *et al.* (2000) Both protein kinase A and mitogen-activated protein kinase are required in the amygdala for the macromolecular synthesis-dependent late phase of long-term potentiation. *J. Neurosci.* 20, 6317–6325
79 Bourtchouladze, R. *et al.* (1998) Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. *Learn. Mem.* 5, 365–374
80 Abeliovich, A. *et al.* (1993) Modified hippocampal long-term potentiation in PKCγ-mutant mice. *Cell* 75, 1253–1262
81 Selcher, J.C. *et al.* (2003) A role for ERK MAP kinase in physiologic temporal integration in hippocampal area CA1. *Learn. Mem.* 10, 26–39
82 Bourtchuladze, R. *et al.* (1994) Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell* 79, 59–68
83 Izquierdo, I. *et al.* (1992) Neurotransmitter receptors involved in post-training memory processing by the amygdala, medial septum and hippocampus of the rat. *Behav. Neural Biol.* 58, 16–26
84 Cammarota, M. *et al.* (2005) Learning twice is different from learning once or from learning more. *Neuroscience* 132, 273–279
85 Micheau, J. and Riedel, G. (1999) Protein kinases: which one is the memory molecule? *Cell Mol. Life Sci.* 55, 534–548
86 Cahill, L. (2003) Similar neural mechanisms for emotion-induced memory impairment and enhancement. *Proc. Natl. Acad. Sci. U. S. A.* 100, 13123–13124
87 Cahill, L. *et al.* (2001) The neurobiology of learning and memory: some reminders to remember. *Trends Neurosci.* 24, 578–581
88 Blair, H.T. *et al.* (2005) The lateral amygdala processes the value of conditioned and unconditioned aversive stimuli. *Neuroscience* 133, 561–569
89 Phelps, E.A. (2004) Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.* 14, 198–202
90 McGaugh, J.L. (2005) Emotional arousal and enhanced amygdala activity: new evidence for the old perseveration–consolidation hypothesis. *Learn. Mem.* 12, 77–79
91 Barros, D.M. *et al.* (2000) Molecular signaling pathways in the cerebral cortex are required for retrieval of one-trial avoidance learning in rats. *Behav. Brain Res.* 114, 183–192
92 Izquierdo, I. (1984) Endogenous state dependency: memory depends on the relation between the neurohumoral and hormonal states present after training and at the time of testing. In *Neurobiology of Learning and Memory* (Lynch, G. *et al.*, eds), pp. 333–350, Guilford Press
93 Izquierdo, I. (1989) Different forms of posttraining memory processing. *Behav. Neural Biol.* 51, 171–202
94 Zornetzer, S. (1978) Neurotransmitter modulation and memory: a new neuropharmacological phrenology? In *Psychopharmacology – A Generation of Progress* (Lipton, M. *et al.*, eds), pp. 78–95, Raven Press
95 Colpaert, F.C. *et al.* (2001) Evidence that amnesic states govern normal and disordered memory. *Behav. Pharmacol.* 12, 575–589
96 Lopez-Salon, M. *et al.* (2001) The ubiquitin–proteasome cascade is required for mammalian long-term memory formation. *Eur. J. Neurosci.* 14, 1820–1826
97 Bramham, C.R. and Messouri, E. (2005) BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog. Neurobiol.* 76, 99–125
98 Alonso, M. *et al.* (2002) BDNF-triggered events in the rat hippocampus are required for both short- and long-term memory formation. *Hippocampus* 12, 551–560
99 Pang, P.T. and Lu, B. (2004) Regulation of late-phase LTP and long-term memory in normal and aging hippocampus: role of secreted proteins tPA and BDNF. *Ageing Res. Rev.* 3, 407–430
100 Izquierdo, I. *et al.* (1997) Sequential involvement of hippocampus and amygdala, entorhinal cortex and parietal cortex in the formation and expression of memory for inhibitory avoidance in rats. *Eur. J. Neurosci.* 9, 786–793
101 Iijima, T. *et al.* (1996) Entorhinal-hippocampal interactions revealed by real-time imaging. *Science* 272, 1176–1179
102 Sacchetti, B. *et al.* (1999) Auditory thalamus, dorsal hippocampus, basolateral amygdala, and perirhinal cortex role in the consolidation of conditioned freezing to context and to acoustic conditioned stimulus in the rat. *J. Neurosci.* 19, 9570–9578
103 Swaab, D.F. (1991) Brain aging and Alzheimer's disease: 'wear and tear' versus use it or lose it. *Neurobiol. Aging* 12, 317–324
104 Paglioli, E. *et al.* (2006) Seizure and memory outcome following temporal lobe surgery: selective compared with nonselective approaches for hippocampal sclerosis. *J. Neurosurg.* 104, 70–78
105 Kensinger, E.A. and Schacter, D.L. (2005) Retrieving accurate and distorted memories: neuroimaging evidence for effects of emotion. *NeuroImage* 27, 167–177
106 Gilboa, A. *et al.* (2006) Mechanisms of spontaneous confabulations: a strategic retrieval account. *Brain* 129, 1399–1414
107 Loftus, J.C. and Palmer, E. (1974) Reconstruction of automobile destruction. *J. Verb. Learn. Verb. Beh.* 13, 585–589
108 Izquierdo, I. and Chaves, M.L.F. (1988) The effect of a non-factual posttraining negative comment on the recall of verbal information. *J. Psychiat. Res.* 22, 165–170
109 Luft, T. *et al.* (2004) Different time course for the memory facilitating effect of bicuculline in the hippocampus, entorhinal cortex, and posterior parietal cortex. *Neurobiol. Learn. Mem.* 82, 52–56
110 Wolfman, C. *et al.* (1994) Intrahippocampal or intra-amygdala infusion of KN62, a specific inhibitor of calcium/calmodulin dependent protein kinase II, causes retrograde amnesia in the rat. *Behav. Neural Biol.* 61, 203–205