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The evidence for hippocampal long-term potentiation as a basis of memory for simple tasks

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ABSTRACT

Long-term potentiation (LTP) is the enhancement of postsynaptic responses for hours, days or weeks following the brief repetitive afferent stimulation of presynaptic afferents. It has been proposed many times over the last 30 years to be the basis of long-term memory. Several recent findings finally supported this hypothesis: a) memory formation of one-trial avoidance learning depends on a series of molecular steps in the CA1 region of the hippocampus almost identical to those of LTP in the same region; b) hippocampal LTP in this region accompanies memory formation of that task and of another similar task. However, CA1 LTP and the accompanying memory processes can be dissociated, and in addition plastic events in several other brain regions (amygdala, entorhinal cortex, parietal cortex) are also necessary for memory formation of the one-trial task, and perhaps of many others.

Key words: long-term potentiation, hippocampus, declarative memory, aversive memory.

INTRODUCTION

Long-term potentiation (LTP) was first described by Bliss and Lomo (1973) and Bliss and Gardner-Medwin (1973) in the dentate gyrus. It was recognized immediately as a possible model of memory, being the only stimulus-induced electrophysiological change that could last as long as a memory (see Matthies 1982, Bliss and Collingridge 1993, Reymann 1993). It consists of the enhancement of a postsynaptic response during many hours, days, or as it was later found, weeks (Barnes 1979) following a brief repetitive afferent stimulation. Subsequently LTP was seen in the CA3 region of the hippocampus (Alger and Teyler 1976), in the CA1 region

(Andersen et al. 1977), in the septo-hippocampal projection (Racine et al. 1983), and then in many regions of the cortex and in other places (Martin et al. 2000, Xin et al. 2006, Maroun 2006). LTP may even kindle silent synapses into action (Kasten et al. 2007). The opposite process, long-term depression (LTD) has also been recognized and proposed to play a role in learning (see Bliss and Collingridge 1993, Ito 2005, 2007, Steuber et al. 2007). It will be dealt with here only passingly. It is very prominent in cerebellum, where it has been best studied.

The widespread existence of LTP strengthened the views linking LTP with memory processes (Teyler and DiScenna 1987, Collingridge 1985, Malinow et al. 1988, Bliss and Collingridge 1993, Reymann 1993, Izquierdo and Medina 1995, 1997, Malenka and Nicholl 1999,

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Kandel and Squire 2000, Malenka 2003, Riedel et al. 2003, Malenka and Bear 2004). Formal theories were put forward in support of the idea that LTP actually underlies, or is an important component of, memory (Lynch and Baudry 1984, Frey and Morris 1997, Martin et al. 2000, Morris 2003, Morris et al. 2003, Martin and Clark 2007). In view of recent developments on the physiology of dendrite responses to different sources of stimulation (Sjöström and Häusser 2006, see also Nicholson et al. 2006), the theory most intriguing and with the largest chance of survival is that of synaptic tagging (Frey and Morris 1997, Morris et al. 2003). It presents a clear-cut physiological explanation of why synaptic activity leading to LTP in one pathway afferent to CA1 can influence synaptic activity brought in by another pathway.

In spite of the criticisms put forward by many (Keith and Rudy 1990, Martínez and Derrick 1996, see Barnes 1996 and Shors and Matzel 1997 for references), the LTP hypothesis of memory held firmly (Izquierdo and Medina 1995, 1997, Martin et al. 2000, Morris et al. 2003) and eventually was proven right (Gruart et al. 2006, Whitlock et al. 2006, Izquierdo et al. 2006). LTP does account for key aspects of memory; although, as will be seen, not all.

THE MOLECULAR BASIS OF CA1 LTP

Many studies have been carried out on the molecular basis of LTP in the CA1 region of the hippocampus and on the role of that region in the memory consolidation of one-trial avoidance learning (see above, and Ahmed and Frey 2005, Izquierdo et al. 2006 for references). The studies show remarkable similarities both in the nature and in the timing of the various molecular changes in LTP and in memory formation (Izquierdo and Medina 1995, 1997, Izquierdo and McGaugh 2000, Izquierdo et al. 2006).

CA1 LTP involves and requires initially an activation of AMPA, metabotropic and NMDA receptors in pyramidal cell synapses (Bliss and Collingridge 1993, Riedel et al. 2003). The induction of LTP is exquisitely sensitive to inhibition by GABAA receptors (see Teyler and DiScenna 1987, Bliss and Collingridge 1993 for references). The AMPA receptor activation depolarizes and thus renders NMDA receptors susceptible to glutamate action and thus permits the entry of Ca^{2+} to the

cell. This causes a release of bound intracellular Ca^{2+} ; the high $[\text{Ca}^{2+}]$ near the synaptic membrane stimulates the local activity of Ca^{2+} -calmodulin-dependent protein kinase II (CaMKII), which promotes the phosphorylation of AMPA and other glutamate receptors (Barriá et al. 1997). Increased Ca^{2+} also occurs presynaptically, in which case it enhances the activity of protein kinase C (PKC), which phosphorylates the protein GAP-43, which further enhances glutamatergic transmission by mobilizing synaptic vesicles (Routtenberg 2000). Postsynaptically, PKC mediates further phosphorylation of glutamate receptors and eventually also the phosphorylation of the cAMP response element binding protein (CREB), a constitutive transcription factor (Roberson et al. 1999, see also Routtenberg 2000). The CaMKII change begins right after induction, and extends for 2-3 h (Barriá et al. 1997). The PKC changes peak at 30 min and extend for 1-2 h (Routtenberg 2000). At 3-4 h from training there is a dopaminergic D1 receptor stimulated increase of cAMP and of the cAMP-dependent protein kinase (PKA), which also phosphorylates CREB (Huang and Kandel 1995). There has been abundant evidence that ERK is activated at about the same time as PKA and that it is also essential for CA1 LTP maintenance and CREB (Selcher et al. 2004). BDNF and ERK may be upstream to mTOR signaling (Bekinschtein et al. 2007b), and which is crucial for hippocampal LTP (Tang et al. 2002).

For a possible role of zif268 in the transition between early and late LTP and in memory formation, see references in Izquierdo and Cammarota (2004). For references on a role of Arc, see Vazdarjanova et al. (2006).

The importance of CREB for the mRNA synthesis and subsequent protein synthesis that have long been held as necessary for the development of enduring neuronal plasticity (Kandel and Squire 2000) or, indeed, enduring memory formation (see Igaz et al. 2002 for references) has been repeatedly demonstrated (Bernabeu et al. 1997, Bozon et al. 2003). The role of mRNA synthesis and protein synthesis in CA1 LTP has been ascertained by numerous studies (see Huang and Kandel 1995). Among the many new proteins that are synthesized in CA1 following LTP or memory processing, there are those that result from the activation of early genes (fos, arc, jun, Src, zif268, etc. see above and Bozon et

al. 2003), and a variety of first glyco- (O'Connell et al. 1997) and then sialoglycoproteins (Foley et al. 2003). These are believed to mold morphological changes at dendritic spines and/or the axon terminals that make synapse with them (see Rose 1995, Foley et al. 2003 for references). Such morphological changes have been suggested repeatedly to underlie the long-term maintenance both of LTP and memory (Kandel and Squire 2000, Bozon et al. 2003, Lynch et al. 2007). Morphological changes of hippocampal synapses (increased cell adhesion, bifurcation, and enlargement of both pre- and postsynaptic components, including receptor area), indeed accompany both LTP (Geinisman 2000) and memory formation processes (O'Connell et al. 1997, Foley et al. 2003). Undoubtedly all these changes suggest enhancement of synaptic function. The brain-derived neurotrophic factor (BDNF) is important for neuritogenesis as a whole, but particularly for the generation of the morphological changes at CA1 synapses that determine long-term maintenance of LTP (Santi et al. 2006, Rex et al. 2007, see also Lynch et al. 2007). The receptor for BDNF is tyrosine kinase B (TrkB) (Yamada and Nabeshima 2003, Brandner 2004), which activates the ERK pathway (Selcher et al. 2004, Sharma et al. 2006). This activation is necessary for the influence of BDNF on neuritogenesis (Alonso et al. 2004).

Granado et al. (2007) showed that D1R but not D5R are critical for hippocampal LTP and for the induction of Zif268 and Arc, proteins required for the transition from early to late LTP to L-LTP and for memory consolidation. For a possible role of zif268 in the transition between early and late LTP and in memory formation, see references in Izquierdo and Cammarota (2004). For references on a role of Arc, see Vazdarjanova et al. (2006).

Thus, the making and maintenance of CA1 LTP result from a well-timed and organized sequence of molecular events initiated by NMDA receptor activation and culminates by morphological changes at particular synapses in CA1 and elsewhere.

THE CHOICE OF ONE-TRIAL AVOIDANCE AS THE TEST MODEL OF THE LTP HYPOTHESIS

One-trial avoidance has long been a favorite for memory consolidation studies for several reasons: a) it is acquired in seconds but may last months (Izquierdo et al.

2003, Frankland et al. 2006), like LTP, b) it requires the participation of CA1, which is the region in which LTP has been best studied (Izquierdo and Medina 1997, Lorenzini et al. 1996); c) it is the task whose pharmacology has also been best studied (Izquierdo and McGaugh 2000), particularly in relation to or in search of a parallel with LTP (Izquierdo and Medina 1995, 1997, Izquierdo et al. 2006, 2007).

Therefore, it is not at all surprising that this task has been chosen as the model to test the LTP hypothesis of memory formation by Izquierdo et al. (2006) and Whitlock et al. (2006).

Other tasks in which the possibility that hippocampal CA1 LTP has also been proposed to play a key role in memory formation include, of course, spatial learning in a water maze (Morris et al. 1986), and classical eye blink conditioning (Tocco et al. 1991). Spatial learning in a water maze (the Morris maze) has long been known to depend on the hippocampus (Morris et al. 1986, 2003). Although the long-term storage of classical eyelid conditioning requires the cerebellum (Krupa and Thompson 1997), the earlier stages of memory formation of this task require alike events in the hippocampus of rabbits (Tocco et al. 1991, 1992). These events (increased AMPA binding) have been also reported after one-trial avoidance in rat CA1-CA3 (Cammarota et al. 1996, Izquierdo et al. 2006).

Due to the multi-trial nature of the task, a role for LTP in spatial learning is difficult to prove (Izquierdo et al. 2006). However, there are many preliminary and scattered findings in favor of such a role in that task (Morris 2003, Morris et al. 2003). On the other hand, a role of LTP of the CA3-CA1 pathway has been recently demonstrated in early classical eye blink conditioning by Gruart et al. (2006).

CA1 LTP IN MEMORY CONSOLIDATION

LTP of CA1 synaptic responses relevant to the memory being made has been recently observed in freely moving rats during consolidation of one-trial inhibitory avoidance (Whitlock et al. 2006). This fits with the simultaneous demonstration that the molecular requirements in CA1 for consolidation of that task are indeed almost if not completely identical to those of CA1 LTP (Izquierdo et al. 2006).

For analogies and correspondences between the mechanisms of CA1 LTP and those observed in CA1 during the consolidation of one-trial inhibitory avoidance, see Reymann (1993) and Izquierdo and Medina (1995, 1997). See also in particular Izquierdo et al. (1992), Jerusalinsky et al. (1992), Bianchin et al. (1994), Cammarota et al. (1996) and specially Riedel et al. (2003) for the involvement of glutamate receptors in CA1; Cammarota et al. (2000) for the dependence of all the enzymatic changes observed (see below) on NMDA receptors activated at the time of training; Cammarota et al. (1997) for the role of PKC and GAP43; Cammarota et al. (1998) for the role of CaMKII; Bernabeu et al. (1997) and Taubenfeld et al. (2001) for the role of the PKA-CREB pathway; Ardenghi et al. (1997) and Bevilacqua et al. (1997) for the role of monoaminergic modulation of PKA (see below); Sweatt (2004), Alonso et al. (2002a, b) and Rossato et al. (2004) for the role of ERKs, which unlike CaMKII (Cammarota et al. 1998, Cammarota and Medina 2004) and PKA (Bernabeu et al. 1997, Vianna and Izquierdo 2004), is apparently related to the aversive aspects of the task (Alonso et al. 2002b), Izquierdo and Cammarota (2004), Bozon et al. (2003) and Vazdarjanova et al. (2006) for the role of early gene products; Igaz et al. (2002) for the need of mRNA and protein synthesis in hippocampus and their timing; Igaz et al. (2004) for posttraining protein synthesis in general (see below); Rose (1995), O'Connell et al. (1997) and specially Foley et al. (2003) for the posttraining role of glyco- and sialoglycoproteins in memory formation; Alonso et al. (2002a, 2005) for the role of BDNF in memory formation and Bekinschtein et al. (2007a) for hippocampal BDNF and memory persistence.

For the role of other enzymes related physiologically to PKC, PKA, CaMKII and the ERKs in memory formation and in LTP (i.e., Juncinase, Src kinase, etc.), see references in Izquierdo et al. (2006), Bevilacqua et al. (2003a, b, 2007). Importantly, mTOR signaling, perhaps stimulated by BDNF and ERKs, is crucial for the consolidation of one-trial avoidance (Bekinschtein 2007b), as has been shown to be crucial for LTP (Tang et al. 2002).

Concerning the genes that are activated and the corresponding proteins that are synthesized in the hippocampus as a consequence of behavioral training and/or memory consolidation, Igaz et al. (2004) have recently ob-

served that CaMKII, Homer 1a, syntaxin 1a and ERK2 must be added to the list. These syntheses might involve reposition of enzymes that had been used by the learning process, or of other constitutive cell elements.

Certainly the observations of CA1 potentiation during classic eye blink conditioning in mice by Gruart et al. (2006) can be taken as a confirmation and an extension of the findings by Izquierdo et al. (2006) and Whitlock et al. (2006) on rat one-trial inhibitory avoidance and vice versa. Together, the three papers have strongly endorsed, to the point of actually proving, the LTP hypothesis of memory formation. (See, however, the last section below).

There have been three recent findings in the eye blink conditioning model. First, it was found that NMDA NR2B receptors in CA1 are involved both in the learning and the LTP that goes with it (Valenzuela-Harrington et al. 2007). These receptors had been previously shown to be involved in both inhibitory avoidance and spatial learning in the same area (Minichiello et al. 1999, Suetake-Koga et al. 2006). Second, it was reported that TrkB is crucially involved both in the eyelid conditioning and in the accompanying LTP (Gruart et al. 2007), as had been previously shown in this and other types of LTP and in avoidance and spatial tasks (see Brandner 2004). Third, and importantly, a dissociation was found in mice that hiperexpress TrkB between eyelid conditioning memory and the accompanying LTP; the former was depressed but the latter was unaltered (Sahun et al. 2007).

The first two findings on eyelid conditioning and CA1 LTP simply update findings in that task concerning both NR2B receptors and TrkB; both proteins have long been to play a key role in LTP and memory formation had been described in other tasks (see, for example, Fox et al. 2006 and Silhol et al. 2007, respectively). The third finding, that of dissociation between LTP and memory, is disquieting but potentially important (see below, last section).

It must be noted that there is much more certainty of the relation between LTP and memory formation at the systems level (see above) than at the cellular level. Given the complexity of the possible interplays between synaptic activation at one particular spine (Sjöström and Häusser 2006, Nicholson et al. 2006), and the possi-

bility that silent synapses are activated by LTP (Kasten et al. 2007). The nature of the message relevant to a particular learning that becomes enhanced by LTP, be it in CA1 or anywhere else for that matter, becomes completely obscure. A possible role of cerebellar Purkinje cell LTD in the recognition of afferent patterns has been suggested by Steuber et al. (2007). Whatever happens in LTD could also happen, theoretically, in LTP; perhaps with a different sign (see Ito 2005, 2007).

It may however be overambitious to propose any such jump to the cellular level from what we know about the fundamental molecular mechanisms of memory in the hippocampus and other brain areas (Izquierdo et al. 2006). We know that the mechanisms of LTP involve protein synthesis leading to changes at synapses that can only be interpreted as underlying strengthening of the transmission across them (see Rose 1995, O'Connell et al. 1997, Geinisman 2000, Geinisman et al. 2004, Foley et al. 2003). This is certainly sufficient as a ground for memory formation and storage and to support general mechanisms and principles of memory storage. How are the changes then transmitted from the hippocampus and related structures to more distant areas of the brain (cerebral cortex, Izquierdo et al. 1997; cerebellum, Krupa and Thompson 1997) is another matter.

In this connection, we are not much better off than the physicians of eighty years ago, who could correctly diagnose that an infectious agent caused pneumonia; but did not know how or why it did, and what treatment to give. The treatments had not been discovered yet; as the pathways that harbor one or other memory have not been shown in detail either.

LTP AND MEMORY OUTSIDE THE HIPPOCAMPUS

There have been postulations of possible LTP in the basolateral amygdala in connection with the consolidation of conditioned fear tasks that require freezing as a response. Several authors proposed that, unlike inhibitory avoidance (McGaugh 2006), conditioned fear tasks that result in acquired freezing consolidate in the basolateral amygdala (Schafe et al. 2005, Wilenski et al. 2006, Phelps 2006). While this position is adhered to by a number of authors (eg., Phelps et al. 2004, Huang and Kandel 2007), it is vigorously contested by others (Vazdarjanova et al. 2001, Cahill et al. 2000, McGaugh,

2006), who advocate for a modulatory influence of the basolateral amygdala in fear- or otherwise aversively-motivated memories. The discussion is not closed. It is possible that the amygdala may use some form or degree of storage in order to fulfill its modulatory role; but the evidence of the amygdala as a storage site is not compelling (see McGaugh 2006). In contrast, the evidence that the hippocampus is a storage site for aversive (Lorenzini et al. 1996, Izquierdo et al. 2006) as well as for a very wide variety of memories is overwhelming indeed. The amygdala as a regulator could be as important as the dopaminergic, noradrenergic and serotonergic pathways that end on D1, beta- and 1A re-ceptors respectively in CA1, the entorhinal cortex, the parietal cortex and other areas that make aversive and other memories. The receptors mentioned modulate cAMP levels and therefore the function of the cAMP-dependent protein kinase (PKA) that is central to memory making in the CA1 area and perhaps in the other regions mentioned as well (Ardenghi et al. 1997, Bevilacqua et al. 1997, Rossato et al. 2004, Izquierdo et al. 2006). Interestingly, neither the monoaminergic pathways nor their receptors, which are strongly linked to the consolidation of emotionally strong memories, including those of aversive nature, modulate memory formation of inhibitory avoidance and other tasks in the basolateral amygdala (Bevilacqua et al. 1997, Rossato et al. 2004, Izquierdo et al. 2006). Highly emotional memories, including aversive or otherwise high attention-demanding memories, are, as known, those best remembered by humans and animals (Hamann et al. 1997, Cahill and McGaugh 1998, Cahill et al. 1999). The dopaminergic D1 positive regulation of one-trial avoidance memory in CA1 has been confirmed by O'Carroll et al. (2006).

The mechanisms of LTP are far from identical in all places. There are important differences between dentate gyrus LTP, which was the first one to be described (Bliss and Lomo 1973), in CA3 LTP (Alger and Teyler 1976), and in CA1 LTP (Huang and Kandel 1995, 1996, see Izquierdo et al. 2006 for references). CA1 LTP is really triggered by glutamate action at NMDA receptors (Bliss and Collingridge 1993); NMDA-independent LTP is instead found in CA3 and elsewhere (Bortolotto et al. 2005). In contrast to the hippocampus, where it has not been described (see Huang and Kandel 1995,

1996) and, if anything, an opposite effect of serotonin might be expected (Bernabeu et al. 1997, Izquierdo et al. 2006), in the amygdala the late maintenance phase of LTP is stimulated by a 5HT₄ mediated mechanism which enhances both PKA and ERK activity (Huang and Kandel 2007). Modulation of this phase depends on dopamine D1 receptors in CA1 (Huang and Kandel 1995) and on β -noradrenergic processes in CA3 (Huang and Kandel 1996). CA3 and various other forms of LTP do not require NMDA receptor activation, which is indispensable for CA1 LTP (see Martin et al. 2000). Muscarinic- or nicotinic receptor-dependent LTP in mammalian ganglia has been described long ago, and seem not to require glutamate receptors at all (see Teyler and DiScenna, 1987). The amygdala and the ventromedial prefrontal cortex have reciprocal pathways that are important for the regulation of memory consolidation (Izquierdo et al. 2007) and extinction (Milad et al. 2007). The prefrontal-amygdala pathway normally generates LTD, which can be reversed into LTP by exposure to stress (Maroun 2006).

ADDITIONAL COMMENT ON AGING AND PRION

There is a decline in cognitive performance in rats and mice between the age of 2-3 months and that of 8 months attributable to a gradually increased sensitivity to down-regulation by the PrPc protein (the physiological prion protein, Coitinho et al. 2003). Coincidentally, both post-tetanic potentiation and LTP in the CA1 region of aging PrP-null mice are also reduced, which has been attributed to increased levels of oxidative stress in aged animals (Curtis et al. 2003). PrPc modulates memory consolidation in CA1 through an interaction with laminin (Coitinho et al. 2006) and with the stress-inducible protein 1 (Coitinho et al. 2007) resulting in changes of PKA and/or ERK function.

Monfort and Felipo (2007) have reported a diminution of the strength of CA1 LTP in normal rats between the age of 2 and 8 months, in which they detected an influence of sex (females were more resistant to the decline).

There are many things that age in the rat or the mouse between the age of 2 or 3 months and that of 8 or 9 months. Since these animals live for over 20-22 months (see Izquierdo et al. 2003), it is perhaps wiser to

ascribe the changes that occur between 2 and 9 months to "maturation" rather than aging. The rift between maturation and aging is, of course, tenuous; and certainly most physiological changes seen in real aging are initiated much earlier. So it is possible that the decline of LTP (Monfort and Felipo 2007), and the decline of memory processes (Coitinho et al. 2003) seen before the age of 9 months may indicate early stages of those seen at an advanced (senile?) age (eg. Barnes 1979, Izquierdo et al. 2003). Sensitivity to regulation by PrPc may be one aspect of this progression.

THERE ARE MORE THINGS

A very large amount of evidence (Izquierdo et al. 1992, Jerusalinsky et al. 1992, Wolfman et al. 1994, Ardenghi et al. 1997, Bevilacqua et al. 1997, Izquierdo and Medina, 1997, Bonini et al. 2003, Rossato et al. 2004, Izquierdo et al. 2006, 2007) shows that glutamate receptor blockers, CaMKII, PKA, ERK inhibitors and other enzyme inhibitors, and a variety of drugs that block memory formation when given into the hippocampus, also block memory formation when given into the basolateral amygdala, entorhinal cortex, posterior parietal cortex and prefrontal cortex. The effect of all these drugs in these other structures has a very different timing from that observed in CA1 and characteristic of LTP. In fact, in all these other structures, the timing of their actions is incompatible with an influence on LTP or an LTP-like mechanism (Izquierdo et al. 2006).

Therefore, it must be concluded that a variety of the mechanisms typical of LTP can act independently of LTP, underlying other forms of plasticity in all the other brain areas mentioned, and that these mechanisms are also essential for the formation of one-trial inhibitory avoidance and perhaps of many other tasks (see above).

The molecular changes that underlie the consolidation of one-trial avoidance (Izquierdo et al. 2006) and other aversive tasks (Matthies 1982) are in general biphasic: there is a rapid posttraining peak of PKA (Bernabeu et al. 1997) and ERK (Alonso et al. 2002b) activity and RNA and protein synthesis (Quevedo et al. 1999, Igaz et al. 2002) followed by and a second peak 2-6 h later (Matthies 1982, Bernabeu et al. 1997, Cammarota et al. 2000, Igaz et al. 2002). The early peak of ERK is probably secondary to the aversive stimuli used for training

(Alonso et al. 2002b). This is different from what is usually assumed to happen in LTP, in which there appears to be just one peak of molecular processes (Malinow et al. 1988), usually believed to be late, at 3-4 h from induction (Huang and Kandel 1995, 1996). Perhaps this difference is not functionally important from the point of view of a role of LTP in memory processing (Izquierdo et al. 2006). Perhaps the rapid early peak has not been sufficiently investigated in LTP; the effect of inhibitors has been much more studied in LTP than the actual biochemical changes.

In addition, the dissociation of CA1 LTP from the classical eye blink conditioning task that was seen in transgenic mice that overexpress TrkB (Sahun et al. 2007) clearly shows that LTP must be regarded not only as "the" mechanism of memory formation. It certainly is one mechanism of memory formation; but not the only one, and in addition LTP can function alone, without lending a basis to memory processes. For roles of LTP in other processes that do not necessarily involve memory formation, see Teyler and DiScenna (1987) and Shors and Matzel (1997).

It has been proposed long ago that different brain structures and processes therein may handle different aspects or components of each memory (Izquierdo et al. 1992, 2006). One-trial inhibitory learning, in spite of its simplicity, involves many such components and several of them can be distinguished mechanistically by different forms of training and treatments (eg. Roesler et al. 2005, 2006). The hippocampus may be in charge of spatial and contextual aspects (Morris et al. 1986, 2003, Martin and Clark 2007); the amygdala may be in charge of highly attentional and/or aversive components (Phelps 2006, see McGaugh 2006); the parietal cortex may be in charge of sensory signals or representations (Izquierdo et al. 2006); etc. It is possible, perhaps very likely, that each of these structures uses a different form of neural plasticity to handle these different components (see Izquierdo et al. 2006). Even within the hippocampal CA1 region NMDA-dependent and NMDA-independent processes can be recognized as separate for different aspects of one-trial memory (Roesler et al. 2005, 2006). The entorhinal cortex, by virtue of its interconnections with all of the areas mentioned (Hyman et al. 1990) may be the main connecting bridge between the various ar-

reas, processes and functions. The famous amnesic case, H.M., who suffered a devastating bilateral temporal lobe surgery in 1953 and was left with an impossibility of making new declarative memories and a pronounced retrograde amnesia was examined by fMRI in 1996 and again last year by Corkin and her group. The lesions of H.M. comprised most if not all the entorhinal cortex on both sides and only part of the hippocampus (Corkin et al. 1997, Salat et al. 2006). In monkeys, too, bilateral entorhinal lesions cause much more amnesia than bilateral hippocampal or hippocampo-amygdalar resection (see Squire et al. 2004 for references). Patients with circumscribed hippocampal surgical lesions because of epilepsy seldom present any amnesia in any way comparable with that of H.M., if they present any amnesia at all (Paglioli et al. 2006). In fact, their postoperative memory performance is usually better than that of their preoperative life, when they were plagued by epileptic seizures (Tuon et al. 2007). Therefore the entorhinal cortex plays a role in memory larger than its fame. At least certainly larger than that of the hippocampus or amygdala.

Of a few things we can be sure. First, that there is LTP in memory, but there is much more to memory than hippocampal LTP. Second, that mechanisms outside the hippocampus are as important as those in that structure, and probably do not involve LTP. Third, that the ultimate storage of memory for weeks, months or years certainly is not in the hippocampus, but elsewhere in the brain, probably in the neocortex or in circuits that heavily involve the neocortex (Izquierdo et al. 1997, Squire et al. 2004). In the case of classic eye blink conditioning, which is made originally in the hippocampus (Tocco et al. 1991, 1992, Gruart et al. 2006, 2007), the ultimate storage is in the cerebellum (Krupa and Thompson 1997). In the case of one-trial avoidance, it is in the neocortex (Izquierdo et al. 1997). Therefore, it is not really necessary, or indeed believable, that the LTP involved in memory acquisition or consolidation should last as long as the memory itself. The search for storage mechanisms continues.

RESUMO

A potenciação de longa duração (LTP) é o aumento de respostas pós-sinápticas durante horas, dias ou semanas após a breve estimulação repetitiva de aferentes pre-sinápticos. Foi pro-

posto durante 30 anos ser a base da memória de longa duração. Vários achados recentes finalmente apoiaram esta hipótese: a) a formação da memória de esquiva inibitória adquirida numa sessão depende de uma cadeia de processos moleculares na região CA1 do hipocampo quase idêntica à da LTP nessa mesma região; b) LTP hipocampal nessa região acompanha a formação da memória dessa tarefa e de outra semelhante. No entanto, a LTP de CA1 e os processos de memória podem ser dissociados e, fora disso, processos plásticos em outras regiões cerebrais (amígdala, córtex entorrinal, córtex parietal) também são necessários para a formação da memória da tarefa de uma sessão e talvez de muitas outras.

Palavras-chave: potenciação de longa duração, hipocampo, memória declarativa, memória aversiva.

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