UNDERSTANDING THE NEUROBIOLOGICAL MECHANISMS OF LEARNING AND MEMORY: MEMORY SYSTEMS OF THE BRAIN, LONG TERM POTENTIATION AND SYNAPTIC PLASTICITY PART III B

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SUMMARY

One of the central issues in neuroscience is concerned with the activity-dependent synaptic plasticity in learning and memory. In such context, changing the strength of synaptic activity between neurons has been widely accepted as the mechanism responsible by which memory traces are encoded and stored in the brain. Thus, the synaptic plasticity and memory hypothesis (SPM hypothesis) shows that activity-dependent synaptic plasticity is induced at appropiate synapses during memory formation, which is essential for information storage for the type of memory involved in the brain area where plasticity is detected or observed. Several criteria and experimental strategies are outlined, and used to investigate this hypothesis. Long-term potentiation (LTP) as an experimental model to study the cellular basis of learning and memory, is one of the most fascinating phenomena that have raised a great interest in neuroscience. LTP is a form of synaptic plasticity that is accepted as a cellular model for stabilization of synapses in several neurobiological events such as development, learning and memory. Defined as the increase in the strength of synaptic transmission observed after tetanic stimulation, this phenomenon can be measured from hours to days, and even outlast the stimulus that induced it over time. The role of LTP in learning has been a central issue in neuroscience, particularly in studies focused on the NMDA receptor-dependent forms of LTP. Thus, much of the experimental work performed in research regarding LTP has been aimed to investigate if LTP equals memory. This review described several properties of synaptic plasticity as well as the neural substrates where synaptic plasticity events are embedded in networks, so as to establish the processing of learning and memory formation.

Key words: Long-term potentiation, long-term depression, synaptic plasticity, synaptic strength, memory, learning, hippocampus, amigdala.

RESUMEN

El fenómeno de LTP es una forma de plasticidad sináptica ampliamente aceptado como un modelo de estabilización de sinapsis en procesos neurobiológicos como el desarrollo del SNC y el fenómeno de aprendizaje y memoria. Desde su descubrimiento por Bliss y Lomo (1973), el fenómeno de potenciación a largo plazo (PLP) o LTP (Long-Term Potentiation, por sus siglas en inglés) ha sido definido convencionalmente como la estimulación aferente de alta frecuencia que es capaz de despolarizar la célula postsináptica, a través de la activación de receptores glutamaérgicos, con la resultante entrada de calcio a la neurona postsináptica. Este evento neurobiológico produce un incremento intracelular en la concentración de calcio [(Ca)i] que induce la activación de diferentes sistemas moleculares de señalamiento intracelular (AMPc, proteínas cinasas, fosforilación de proteínas intracelulares) que conlleva a una alteración de la actividad postsináptica y/o presináptica, dando por resultado un persistente incremento de respuesta sináptica específica dependiente de la activación del receptor glutamaérgico NMDA. Un alto porcentaje de los resultados experimentales relativos al fenómeno de LTP se ha centrado en las formas de LTP dependientes de la activación y función de este subtipo de receptor glutamaérgico, particularmente en la corteza cerebral, la formación hipocampal y las estructuras amigdalinas, estructuras neuroanatómicas que conforman el sistema límbico en los mamíferos. Sin embargo, han surgido muchas interrogantes cuando se trata de igualar los eventos experimentales observados, del LTP, con los eventos de memoria que ocurren en el cerebro de los mamíferos. Por ejemplo, de estas interrogantes podemos mencionar la relación que guardan las propiedades analizadas del LTP con respecto a la función de la memoria, qué tipos de aprendizaje están relacionados con el desarrollo del fenómeno de LTP y que áreas cerebrales se involucran en el desarrollo de este proceso. Si el

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fenómeno del LTP juega un papel relevante en el desarrollo de la memoria, se debería postular, en principio, que la actividad-dependiente de la plasticidad sináptica y las diferentes formas de expresión de memoria que existen en el cerebro, comparten un denominador común. Es decir, que la actividad resultante de la plasticidad sináptica es inducida en sinapsis apropiadas durante la formación de cualquier evento o fenómeno de memoria analizado. Este proceso neurobiológico debe ser relevante y suficiente para almacenar la información pertinente al tipo de memoria mediada por una región cerebral específica, en la que ocurre un evento de plasticidad sináptica. La plasticidad sináptica es un evento neurofisiológico que induce patrones específicos en la actividad neuronal, mediado por eventos neuroquímicos y mecanismos moleculares que, finalmente, conllevan a la generación de cambios en la excitabilidad neuronal y en la eficacia sináptica y que permanecen por muy largo tiempo y perduran indefinidamente en relación con los eventos neurobiológicos que los suscitan. En este contexto, se puede resumir que, tomando como base las propiedades de la plasticidad sináptica, el fenómeno de LTP, el fenómeno de DAP (depresión a largo plazo) o LTD (Long-Term Depression, por sus siglas en inglés) constituyen los modelos fisiológicos más viables y apropiados en la generación de diferentes sistemas de generación de memoria, tales como la codificación y almacenamiento de información y la consolidación de trazos de memoria perdurables en el tiempo. Diversos estudios experimentales han demostrado que el procesamiento de memoria establecido por los mecanismos neurobiológicos que inducen y mantienen el fenómeno de LTP o LTD, ocurre a través de la activación de circuitos neuronales específicos. En tales circuitos, la codificación y almacenamiento de información (trazos de memoria) ocurre como producto de las propiedades de los circuitos neuronales involucrados y no exclusivamente debido a mecanismos operantes en sinapsis individuales. Por ejemplo, el tipo de información procesada en el hipocampo difiere de la información procesada en la amígdala. En esta última la información procesada, codificada y almacenada, permanece en función del tiempo como respuesta de la conservación de los mecanismos biológicos de plasticidad neuronal que operan en los circuitos neuronales activos, y que están presentes en ambas estructuras. Más aún, es importante mencionar que la hipótesis de "PLASTICIDAD SINAPTICA-MEMORIA" o SPM *(Synaptic Plasticity and Memory hypothesis)* propone que los mecanismos mediados por LTP soslayan procesos cognoscitivos, tales como la atención (evento psicobiológico indispensable) requeridos para el procesamiento del fenómeno de aprendizaje. Se han establecido diversos criterios neurofisiológicos para estudiar y evaluar la hipótesis de la "PLASTICIDAD SINÁPTICA-MEMORIA" (SPM) en el cerebro de los mamíferos. Tales criterios permiten relacionar la propiedad de la plasticidad sináptica con los eventos fisiológicos de aprendizaje y memoria, empleando diferentes parámetros y estrategias experimentales. Es decir que esta hipótesis postula que, a nivel experimental, es posible detectar correlaciones entre la expresión de un evento de aprendizaje y los cambios funcionales de plasticidad sináptica. Asimismo, la inducción de cambios cuantificables de plasticidad sináptica, detectados en sinapsis específicas en diferentes sistemas neuronales, debe estar asociada a procesos de aprendizaje y memoria. Del mismo modo, cualquier intervención o manipulación experimental (sea esta de naturaleza farmacológica, molecular o genética) deberá mostrar un efecto cuantificable sobre cualquier proceso de memoria y aprendizaje, mediado a través de la facilitación o bloqueo de la actividad sináptica o de la eficacia sináptica resultante.

Diversos estudios electrofisiológicos han demostrado que los mecanismos neuronales involucrados, tanto en la inducción del fenómeno de LTP como del fenómeno del LTD, en diferentes regiones del hipocampo, pueden ser dependientes o independientes del receptor glutamaérgico, NMDA; pero ambos eventos implican la relación de la actividad presináptica con una despolarización o hiperpolarización de la neurona postsináptica. Más aún, dependiendo del grado de estimulación de los circuitos neuronales, responsables de inducir cambios en la actividad sináptica o incrementos de la eficacia sináptica, en intervalos de tiempo definidos, en las sinapsis de las neuronas operantes, pueden detectarse cambios en la respuesta en la actividad sináptica. Dichos cambios ocurren ocasionalmente (en una sola ocasión), con posterioridad a los procesos de estimulación por el contacto entre neuronas presinápticas y postsinápticas. Estos resultados han permitido postular, empleando modelos de circuitos neuronales funcionales, la hipótesis sobre la existencia de "sinapsis silentes o silenciosas". Esta hipótesis explica la transformación de sinapsis inactivas en sinapsis activas mediante la síntesis e inserción de diferentes subtipos de receptores glutamaérgicos, por ejemplo, el subtipo de receptor AMPA que permite sustentar la vieja teoría sobre la expresión del fenómeno de LTP. Más aún, estudios recientes han demostrado que la persistencia del fenómeno del LTP, en sistemas neuronales en el SNC de mamíferos, es producto tanto de la continua activación del receptor glutamaérgico, NMDA, como de la síntesis *de novo* de proteínas intracelulares esenciales que consolidan los eventos de plasticidad sináptica dependientes de LTP. En el contexto de la plasticidad sináptica relacionada con los eventos biológicos de memoria y aprendizaje, estudios recientes han demostrado que múltiples circuitos neuronales expresan eventos de plasticidad sináptica a corto plazo *(short-term plasticity),* lo que resulta de la ubicuidad de estos eventos en el cerebro de los mamíferos y de especies no mamíferas. Si bien estos resultados muestran por vez primera la ubicuidad de este fenómeno, también han permitido postular una nueva hipótesis que describe que este evento de plasticidad cerebral (*v.g.*, facilitación o depresión a corto plazo) parece contribuir de forma relevante a los procesos funcionales de filtración para el procesamiento de la información y a la consolidación de diferentes formas complejas de memoria y aprendizaje.

Palabras clave: Potenciación a largo plazo, depresión a largo plazo, plasticidad sináptica, memoria, aprendizaje, hipocampo, amígdala.

SYNAPTIC PLASTICITY AND LONG-TERM POTENTIATION: NEW HYPOTHESIS AND FINDINGS

From the original discovery made by Bliss and Lomo (1973), long-term potentiation (LTP) has been captured as one possible synaptic mechanism of learning and memory as neurophysiologists enunciated 15 years after the first description of LTP, as "the most dramatic example of neural activity" (Bliss, 1990; Bliss et al., 1990). LTP is a form of synaptic plasticity widely accepted as a cellular model for stabilization of

synapses in neurobiological phenomena such as development and learning and memory (Harris, 1995). Conventional definition of LTP could be briefly mentioned as follows: *High-frequency afferent stimulation depolarizes a postsynaptic cell through activation of glutamate receptors with a resultant calcium ion (Ca^{2+}) influx into the post-synaptic neuron. As a result, the rise in intracellular calcium concentration stimulates various intermediary intracellular signaling molecules (cAMP, protein kinases, which leads to an alteration of the post-synaptic function (enhanced glutamate receptor function) and/or pre-synaptic alteration (increased neurotransmitter release) which results in a persistent synaptic–specific N-methyl-D-aspartate receptor (NMDA)-dependent enhancement response* (McEachern and Shaw, 1996). Much of the experimental work concerning LTP in learning has been focused on the NMDA receptor-dependent forms of LTP (Martin et al., 2000).

But several questions have arisen regarding the issue if LTP equals memory (Stevens, 1998). In order to qualify LTP as memory, one must address several questions before emphasizing such issue. Some pertinent questions as, what type and what properties of LTP are really relevant to memory? Is the long-term depression or depotentiation involved in the memory process as well? What types of learning are involved related with LTP formation? And what brain areas are involved in such processes? One important issue to ask is if LTP is relevant to encoding, storage, consolidation and retrieval, or if it just applies to one aspect of these memory processes (Martin et al., 2000). Thus, if LTP has a real role in memory, a more appropriate hypothesis should be stated by postulating that activity-dependent synaptic plasticity and multiple forms of memory known to exist (Kandel & Schwartz, 1982; Lynch and Braudry, 1984). Morris & Frey (1997) share a common core; that is the synaptic plasticity and memory hypothesis (or SPM) states that *activity dependent synaptic plasticity is induced at appropriate synapses during memory formation. Such process is relevant and sufficient for information storage underlying the type of memory mediated by any specific brain area in which plasticity occurs* (Martin et al., 2000).

Synaptic plasticity is a physiological phenomenon that induces specific patterns of neural activity sustained by chemical and molecular mechanisms. This gives rise to changes in synaptic efficacy and neural excitability which outlast for a long time the events that trigger them (Martin et al., 2000). According to several properties of synaptic plasticity previously reported and recently discovered, make LTP suitable in development of several memory systems, such as initial encoding and storage of memory traces and initial phases of trace consolidation over time (Martin et al., 2000). Such memory processing induced by LTP or LTD, most probably occurs as a network specific process, making LTP a universal mechanism for encoding and storing memory traces. Whatever is encoded is part of a network property rather than mechanisms working at individual synapses (Martin et al., 2000). For instance, the type of information processed at the hippocampus is quite different from the information processed by the amygdala, and such information should remain, if the mechanisms of plasticity operating in each brain area are conserved (Martin et al., 2000).

Moreover, if synaptic plasticity is involved in encoding and storing, different patterns of neural activity should be required for the reading-in and reading-out stages (Bursaki, 1989; Hasselmo et al., 1995; Churchland & Sejnowski, 1992).

SPM hypothesis(Synaptic plasticity and Memory hypothesis) should also be distinguished from several hypothesis previously postulated such as the "null hypothesis", which states that synaptic plasticity has nothing to do with memory (McEachern & Shaw, 1996), or the notion that synaptic plasticity plays a role in attention processing, rather than memory (Shors & Mazel, 1997). It is quite important to mention that SPM hypothesis *supports the view that LTP-like mechanisms underlies cognitive processes, such as attention, which is a basic pre-requisite for learning processing* (Martin et al., 2000) (see criteria for assessment of the SPM hypothesis in table 1). Moreover, several reports have demonstrated that most of the research that has been used to evaluate and assess the SPM hypothesis has been based on the following different experimental strategies (Martin et al., 2000):

a) *Correlation:* an experimental strategy employed to detect correlations between behavioral parameters of learning with some of the functional properties of synaptic plasticity;

b) *Induction:* induction of measurable changes in synaptic efficiency occurring in specific synapses of appropriate neural networks of the brain should be associated by learning processing and experience. Thus, induction of synaptic changes in relevant synapses should result in memories;

c) *Occlusion:* saturation of synaptic plasticity in a specific neural network should be able to obliterate traces of corresponding memories previously consolidated, producing an occlusion of the encoding of new memories;

d) *Intervention:* experimental manipulations based on the employment of any pharmacological, molecular,

TABLE 1
Criteria established to assess SPM hypothesis.

DETECTABILITY: meaning that if animals display memory of any previous experience, lasting any length of time, a change in synaptic efficacy (expressed as LTP or LTD) should be detectable somewhere in the CNS, in specific synapses in one or more brain areas. Due to the paucity of synapses that change over time with learning experience and to their localization in the brain, this criterion is made difficult to meet by experimental basis (Martin et al., 2000).

MIMICRY: If changes in synaptic efficacy are the neural basis of trace storage, hypothetical induction of specific spatial pattern of synaptic changes should therefore, give rise to an apparent memory for any past learning experience that in practice never occurs. This criterion opposes the former because inducing changes in synapses must be sufficient to induce a memory trace. Thus, inducing LTP or LTD in a particular subset of hippocampal synapses to achieve an apparent kind of memory of an event that never transpired, is unlikely to occur in the near future. However, it has been shown, that repeated acoustic stimuli induces LTP at inhibitory synapses (Mauthner cell), inducing a behavioral desensitization of the escape reflex in the goldfish (Oda et al., 1998). Therefore artificial induction of LTP at specific synapses may produce specific changes in behavioral response, as is the case of behavioral desensitization (Martin et al., 2000).

ANTEROGRADE ALTERATION: Several mechanisms are required to induce changes in synaptic weights; interventions that impair or prevent induction of such synaptic changes during learning experience, in principle must impair animal´s memory of that experience. Thus, blockage of the mechanisms that induce synaptic changes during learning has an anterograde effect of impairing a new learning (Martin et al., 2000).

RETROGRADE ALTERATION: Alteration of the pattern of synaptic weights after learning, in principle affects animal's memory for a particular past experience. Thus, interventions that modify the spatial distribution of synaptic changes induced by prior experience should alter the animal's memory of that experience (Martin et al., 2000).

genetic or any other interventions, will have a commensurate effect on learning and memory, either by enhancing or blocking the synaptic activity,

e) *Erasure:* erasure of synaptic plasticity, shortly after learning, should be able to induce forgetting.

SYNAPTIC PLASTICITY PROPERTIES AND ITS ROLE IN LEARNING

Various forms of synaptic plasticity have been shown to differ in regard to their persistency over time, as well as their mechanisms of induction (e.g., by learning experience) and mechanisms of expression. Long-term potentiation (LTP) is the best known example (Bliss and Lomo, 1973) where synaptic potentials, evoked by low frequency stimulation, are observed to increase in amplitude as a result of brief patterns of high-stimulation, or the pairing of pre-synaptic activity with post-synaptic depolarization (figure 1a). As far as we know, LTP occurs in different pathways of the brain besides the areas where this phenomenon was observed firstly (e.g., dentate gyrus and hippocampus). Most forms of LTP are known to be glutamaergic and most of them appear to be induced following activation of the N-methyl-D-aspartate (NMDA) receptor. Several electrophysiological studies demonstrated that LTP induction and the neural mechanism involved are both LTP-NMDA-dependent and LTP-NMDA-independent (Martin et al., 2000). Counter wise, long-term- depression (LTD), first discovered in CA1 field *in vitro*, is a long lasting activity dependent decrease in synaptic efficacy (Lynch et al., 1977). Both hetero and homosynaptic forms of LTD have been shown to be induced in various pathways of the hippocampal formation *in vivo* (Levy & Steward, 1979; Thiels et al., 1994; Heinen et al., 1996), and *in vitro* (Dunwiddie & Lynch, 1978; Dudek & Bear, 1992; Derrick & Martinez, 1996) (Figure 1b). Similar to LTP, LTD induction has been shown to be NMDA-receptor dependent or independent, and occurs in different areas of the brain such as the amygdala (Li et al., 1998) and the cortex (Artola et al., 1990; Kirkwood and Bear, 1994). In general, the terms of LTP and LTD refer respectively to input–specific up or down–regulation of synaptic strength, lasting at least for 1 h, regardless of the NMDA-receptor dependent or independent activity forms (Martin et al., 2000).

Other forms of synaptic plasticity, namely, *depotentiation* or the *reversal of LTP* have been shown to occur *in vivo* (Staübli & Lynch, 1990) and *in vitro* (Fujii et al., 1991, Bashir & Collingridge, 1994). Although several theoretical arguments have assigned different biological functions to both LTP and LTD (e.g., learning and attention for LTP; forgetting for LTD) (Willshaw & Dayan, 1990), recent experiments have shown that actually they complement each other in regard to signal-to-noise, meaning that they might work and regulate storage capacity (Martin et al., 2000).

In such context, several arguments have pointed out that synaptic plasticity displays physiological properties, suggestive of an information device (McNaughton, 1983; Lynch & Braudry, 1984; Mooris et al., 1989b; Bliss & Collingridge, 1993; Barnes, 1995; Shors & Matzel, 1997). Thus, several experimental works have shown that the properties of such information device include a NMDA-receptor dependent LTP form, whose induction is associative (i.e., learning should be associated with induction of measurable changes in synaptic strength in specific networks of the brain at relevant synapses) and its expression is input-specific and persists over time (Martin et al., 2000). Thus, such neurophysiological properties seem to be relevant for *associative learning and other features regarding learning and memory processing* (i.e., its induction is capable of associating different independent patterns of both pre-synaptic

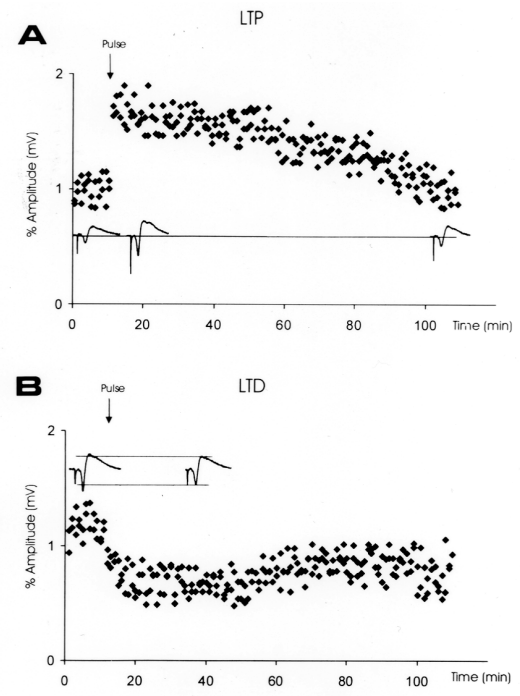

Fig. 1. Schematic representation of Long Term Potentiation (LTP) and Long Term Depression (LTD) phenomena in CA1 field in the hippocampus of the rat.
(A) Shows the induction of the Long-term Potentiation phenomena after Schaffer Collateral pathway stimulation with a 100 Hz train stimuli (tetanized pulse) applied for 1s at arrow. Responses were recorded from a population of pyramidal cell in the CA1 hippocampal field. The graph depicts the increase of field postsynaptic potentials (fPSPs) (plotted as % amplitude from baseline) as a function of time and the recovery of the activity over time. Insets show the field potentials fPSPS at different times describing the induction of LTP process. Note the increment on the amplitude of such potentials (fPSPs) after tetanic stimulation as compared to control. Such increment in the slope of the fPSPs amplitude reflects the magnitude of the change of the synaptic efficacy between neurons. **(B)** Shows the Long-term Depression phenomena (LTD) in same hippocampal field as described above for LTP. This graph depicts the decreased of fPSPs (% amplitude) as a function of time, after 100 Hz train stimuli was delivered to Schaffer collateral pathway/ CA1 pyramidal cell (at arrow), similar to what is shown in A. Insets show the fPSPs at different times. Note the decrement of the field potentials after delivery of stimuli to CA1 region as compared to control. Such decrement in the slope of the fPSPs amplitude reflects a change in synaptic efficacy among cells.

and post-synaptic neural activities); *storage capacity* (i.e., specific synaptic mechanism endows greater storage capacity as compared to changes in cell excitability) and long lasting memory (i.e., synaptic changes and synaptic enhancement must endure as long as memory) (Martin et al., 2000).

a) Properties of LTP: implications with memory processing. Newly discovered properties of synaptic plasticity have been added and implicated in the SPM hypothesis, which include metaplasticity, induction of LTP and LTD by natural patterns of stimulation and the role of post-synaptic dendritic action potentials in neuronal propagation of both forms, synaptic gain or redistribution, degree of input specificity, potentiation of individual synapses, expression of silent synapses and variable persistence of LTP following identical condition of induction (for detailed information and specific references, see Martin et al., 2000).

1. Metaplasticity. The magnitude and direction of a synaptic change can be influenced by a prior history of synaptic activity. Such prior activity can alter the capacity of a synapse to undergo a plastic change in the future (Abraham, 1996; Abraham & Bear, 1996). For example, prior tetanization (required to induce LTP) can inhibit subsequent LTP formation and facilitate LTD expression (Martin et al., 2000). It has been postulated that low levels of post-synaptic activity might result in LTD (according to theoretical descriptions of such metaplasticity property) and high levels of post-synaptic activity might result in LTP. Neurochemical events related with the autophosphorylation of the Ca^{2+}/CaM-dependent kinase (CaMK-II) have been implicated in metaplasticity (Bear, 1995; Mayford et al., 1995, 1996; Thompa & Friedrich, 1998). Activation of both NMDA receptor dependent–LTP and metabotropic glutamate receptors are regulated by different activities of CaM/ protein kinases as occurs both *in vivo* and *in vitro* (Martin et al., 2000). Moreover, stress hormones have been found to induce metaplastic changes at specific synapses at the hippocampus and amygdala (Li et al., 1998). For instance, stressed animals show impaired LTP induction and LTD facilitation, an effect that seems to depend on glucocorticoid receptor induction (Xu et al., 1997; Kim & Yoon, 1998).

2. Patterns of Induction. Methods used to induce LTP based on the application of long bursts of presynaptic stimuli at high frequencies or to induce LTD throughout long periods of low frequency stimulation, do not emulate the natural pattern of neuronal activity. However, in the hippocampus, both LTP, LTD and depotentiation can be induced with stimuli that emulates the firing pattern of neurons associated with the normal theta rhythm occurring in animals during moving and exploring their environment (Martin et al., 2001). Several experiments have demonstrated that LTP can be induced by delivering short bursts of 100 Hz-stimulation at intervals of 200 ms, synaptic potentiation that lasts at least for several weeks (Larson et al., 1986). Moreover, LTP can be induced by burst stimulation in the theta rhythm in anaesthetized rats (Pavlides et al., 1988). *In vitro*, it has been demonstrated that CA1 slices bathed in carbachol (in order to induce theta rhythm) can induce long lasting LTP after trains of single pulses are locked to the positive theta peak an stimulation on the negative

phase of the rhythm had no effect or rarely induced depression of synaptic activity, namely, LTD (Huerta & Lisman, 1993). Moreover, depotentiation of already established LTP was shown to occur *in vitro*, after a single burst or a train of single pulses were locked to the negative phase of the theta rhythm (Huerta & Lisman, 1995, 1996). Similar results have been found *in vivo* in the CA1 field of the hippocampal formation (Holscher et al., 1997). Moreover, several studies have confirmed that LTD can be induced by brief periods of stimulation at 1 Hz paired with mild post-synaptic depolarization (Wang et al., 1997). Recently, it has been shown that back-propagating dendritic action potentials, between bidirectionally connected slices of neocortical tissue, are necessary to induce synaptic plasticity (Markram et al., 1997). Synaptic strength was potentiated when the EPSP (excitatory post-synaptic potentials) preceded the back-propagating dendritic spikes by 10 ms, and counterwise, synaptic efficacy was depressed when dendritic spike preceded EPSP (Markram et al., 1997). For instance, in the CA1 hippocampal region, bursts of post-synaptic action potentials are required for the induction of synaptic potentiation *in vitro* (Thomas et al., 1998; Pike et al., 1999). Thus, timing of post-synaptic action potentials plays a critical role in inducing synaptic changes and plasticity in specific bidirectional connected neurons (figure 2) (Martin et al., 2000).

3. Temporal distribution and input specificity. Tetanization paradigms commonly used for LTP induction have frequently been criticized for being non-physiological. In this regard, while pre-synaptic fibers are commonly stimulated with single low frequency pulses, hipoccampal and cortical neurons show high frequency bursts when firing. Mimicking such bursts, post-synaptic neurons respond to a train

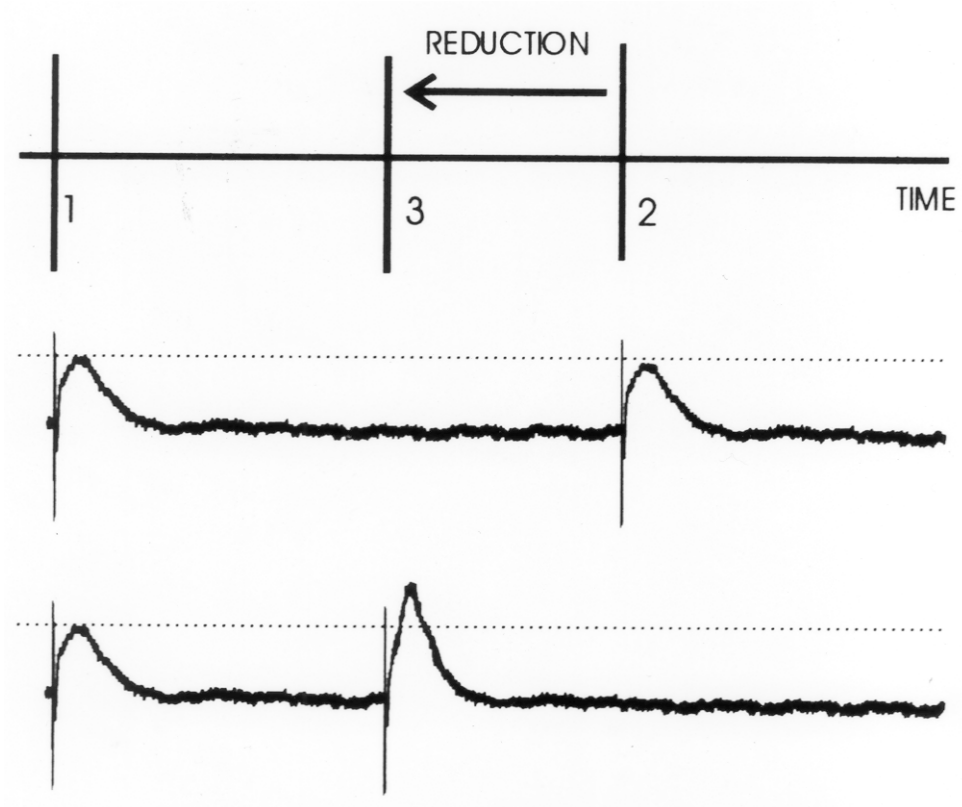

Fig. 2. Schematic representation of Paired Pulse Facilitation (PPF) in the CA1 field in the hippocampus of rat. Paired pulse facilitation was obtained after Schaffer Collateral pathway stimulation and responses recorded after placing intracellular electrodes in isolated hippocampal tissue bath with artificial Ringer-Krebs solution. Top panel shows the stimulation protocol, which describes the distance among (time interval) the pulse stimulation at elected times. Thus, a pulse stimulus of 0.1 ms was initially delivered to the cell at point (1). After a brief period of time (100 ms) a second stimulus (test stimulus) (2) of same magnitude was delivered to same cell, and the excitatory postsynaptic potentials (EPSPs) responses (middle panel) were recorded at respective time intervals of paired pulse stimulation (interval delay 1-2, and recorded responses are referred to interval delay 1-2). Note that no significant changes in the amplitude of the recorded EPSP responses are shown at this interval delay. When this time interval of paired pulse stimulation is reduced to point (3) (interval delay 1-3) a significant increase in amplitude of recorded EPSP responses is obtained as shown in the bottom panel. This figure illustrates that the reduction of the time interval delay (from 1-2 to 1-3) induce facilitation at synapses after paired pulse stimulation of pyramidal cell distant among the time interval.

of action potentials showing a frequency-dependent short-term depression in the neocortex. Thus, after LTP induction, the first EPSP (excitatory post-synaptic potentials) results to be potentiated, but in general the train of post-synaptic action potentials showed an enhanced depression without changing the overall throughput (Markram and Tsodys, 1996). These experimental observations led to the argumentation that the redistribution of synaptic efficacy changes the content and does not result in a gain of the signal (Martin et al., 2000). Contrary to this situation, LTP induction in hippocampal synapses (e.g., CA3-CA1 synapses) produces a similar EPSPs enhanced response throughout the train, irrespective of the short-term depression, resulting in an overall increased gain (Selig et al., 1999). Thus, differences in the way cortical and hippocampal synapses response reflect differences in LTP expression mechanisms (Martin et al., 2000). Another novel property of LTP, which challenges its classical properties, is that input specificity of LTP does not require active synapses (Engerbert and Bonhoeffer, 1997). Results obtained from LTP induction in organotypic cultures have shown that LTP spreads out in active synapses as well as in inactive synapses in the same cell (Engerbert and Bonhoeffer, 1997). Although this explanation still needs to be clarified, LTP induction seems to be distributed to nearby inactive synaptic terminals besides active ones (Martin et al., 2000).

4. Synaptic change, silent synapses and synaptic tagging. Several reports have shown that LTP can be expressed at individual neurons in an all-or-none fashion (Petersen et al., 1998). In such context, when LTP is induced by pairing of pre-synaptic activity to post-synaptic depolarization, the activity dependent response of active synapses shows an expected gradual increase in synaptic efficacy over time. But when minimal stimulation is applied, some individual synapses show a response change (digital change) that occurs only once, at different thresholds, during the sequence of pairings (Petersen et al., 1998). Although several explanations have been given for such findings, based on neural networks models (e.g., synapses flip from non-potentiated to a potentiated state, helping them to separate circumstances in which information is stored or not stored) (Martin et al., 2000). It has been suggested that such findings might result from transformation of "silent synapses" to active-communicative synapses by insertion of new glutamaergic-AMPA receptor subtypes (Liao et al., 1995; Isaac et al., 1995; Kullmann, 1994). This proposal supports early theories regarding the expression of LTP (Lynch & Braudry, 1984). Moreover, the temporal persistence of LTP has been explained on the basis of the continuous NMDA receptor activation and protein synthesis as well (Malenka, 1991; Goelet et al., 1986). One idea given to explain LTP persistence is based on the concept that right after LTP induction (early LTP), there is a temporal window where protein synthesis-independent LTP is consolidated by a protein dependent–plastic activity (Nguyen et al., 1994). Thus, several questions arise conceptualizing this idea. For instance, how this protein dependent-plastic activity is selectively targeted to active synapses during tetanization (Martin et al., 2000). In order to solve this puzzle, researchers (Frey & Morris, 1997) have brought out a new concept introduced as *synaptic tagging*. This concept is based on the idea that proteins involved in synaptic plasticity and initially synthesized in the cell body, as a result of dendritic activation from various inputs (not necessarily through activation of glutamaergic receptors), could be randomly distributed in non-targeted sites. Thus, opposite to the conceptualized idea that individual proteins being trafficked to newly potentiated synapses, LTP induction would tag those synapses, which would be able to recruit diffusely targeted proteins. Once that this proteins have been sequestered, they would be able to consolidate the synaptic potentiation in an input-specific manner (Martin et al., 2000). This hypothesis has been recently shown to occur after strong potentiation was introduced in one afferent pathway in adult brain slices, in order to induce protein synthesis-dependent LTP (defined as late LTP), while a second afferent input was exposed to tetanization stimuli, 60 min later, shortly after inhibiting the synthesis of protein by application of anisomycin (Frey & Morris, 1997). Unexpectedly, late LTP was observed in both pathway-tetanized prior to protein synthesis inhibition and in the second neural pathway where protein synthesis was inhibited but tetanized as well (Frey & Morris, 1997). Moreover, such findings were shown even to occur if second input was exposed to a weakly stimulation period to induce a late-LTP response on its own, and/or after weak stimulation for up to 2 hr before induction of late LTP in the other neural pathway (Frey & Morris, 1998a). Such important results implicate that persistence of LTP over time seems to depend on the history (past and future) of activation of the whole neuron, and not just on conditions prevailing during LTP induction *per se* (Frey & Morris, 1998b). How could these findings fit the SPM hypothesis as explained above? When an animal attends novel events, LTP induction will appear in a subset of hippocampal synapses, which will show relatively rapid time-course decay over time. Therefore, LTP consolidation will occur in those synapses that have been potentiated, either before or after the cellular mechanisms that

bought out the neuronal activation of the specific cell that triggered the synthesis of related proteins involved in synaptic-induced plastic changes. Thus, such neural-related mechanisms could be set forward in important neural structures when a significant input (e.g., emotional from amygdala inputs or a highly motivational event from cortical inputs) in mammal species is motivated to learn (Martin et al., 2000). For instance, synaptic tagging could well be explained to occur in freely moving thirsty rats whose LTP was reinforced by water reward right after its induction (Seidenbecher et al., 1995), or in animals undergoing post-trial drug administration or electrical stimulation (McGaugh et al., 1966; Martin et al, 2000).

NEURAL REPRESENTATION OF INFORMATION STORED BY DIFFERENT MEMORY SYSTEMS

Synaptic plasticity plays a crucial role in distinct memory systems of the brain comprised in different neural structures using the NMDA-dependent LTP system to encode and store different types of information in the neural network employed (Martin et al., 2000). The direction of change of a synaptic plasticity event often correlates with the direction of change of an overt expression of a determined behavior, as occurs in simple neural networks. For instance, condition experimental procedures commonly used to induce the strengthening or weakening of specific neural responses, as well as by either synaptic facilitation or depression, respectively, are usually determined by the direction of the synaptic plastic changes that ultimately will be reflected in the overt expression of behavioral responses (Hawkins & Kandel, 1994). However, in complex neural networks this events might not prevail, due to the fact that a huge gap exists from on-going synaptic events to the function of a neural network and, finally, to the expression of the animal behavior. Nevertheless, synaptic plasticity is a reflection not only of the resultant activity of the direction of the change, but much more, it indicates that a newly emergent property as a result of the plasticity change is occurring within a network itself (Morris, 1990). Thus, take for example a simple neural network, which is normally involved in a simple neural reflex response. What this neural network does is just to increase or decrease the throughput of neural signals (Martin et al., 2000). These neural networks, as complicated as they may be, structurally are comprised with excitatory, inhibitory and facilitatory neurons in different arrangements that encode information about learning experience in an indirect manner. This means, that learning experience produces changes in the adaptive animal behavior output, and does not represent the specific learning experience that would induce the pertinent changes that would associate them to be explicitly recalled (Martin et al., 2000). Conversely, changes in synaptic efficacy increase the probability that behavioral output will be appropriate for dealing with similar situations when present in the future. For instance, in classical conditioning, a neutral stimulus (CS) repeatedly paired with a biologically significant unconditioned stimulus (US) eventually will evoke a condition response brought out by the CS. Thus, the neurobiological mechanism mediating such response (the probability and magnitude of the response) would result either in the increases of synaptic efficacy (such as pre-synaptic facilitation or LTP) or from neuronal excitability (EPSP-spike potentiation) (Hawkins & Kandel, 1984). Although, modern psychological theories recognize the associative conditioning processing as a set of procedures that potentially involve different types of learning processes (Rescola & Wagner, 1972). In such context, information must first be represented in a distributed manner enabling multiple associations to be overlaid within a neural structure of synaptic connections. Thus, information represented in this manner would be suitable for the brain to process sensory, motor, and learning-related neural circuits, enabling coded information to be used inferentially and the events that enter into association would be recalled explicitly (Martin et al., 2000). Moreover, the associative process would require also an error-correcting learning process (Rescola & Wagner, 1972).

HIPPOCAMPAL FORMATION-DEPENDENT LEARNING AND SYNAPTIC PLASTICITY

LTP studies performed at the perforant path-dentate gyrus granule cell, as well as at the Schaffer collateral-CA1 pyramidal cells synapses (figure 1 in previous chapter IIIa) demonstrated that the LTP activity resulted as an NMDA receptor dependent form. Similar circumstances showing LTP in synapses of the perforant path onto CA3 pyramidal cell, including the interconnecting CA3 neurons through the longitudinal-commisural pathway, but not with mossy fibers synapses onto CA3 neurons, resulted in a NMDA-receptor independent form of LTP (figure 3) (Martin et al., 2000). Most of the initial studies implicating LTP in memory were merely based on correlation. In such context, different experimental works showed that persistence of LTP was statistically correlated with the rate of learning and degree of retention of spatial

memories over time with relation to aging (Barnes & McNaughton, 1985). In another set of experiments, similar correlations were reported showing that over expression of the mutant amyloid precursor protein (APP) in the murine model of Alzheimer's disease (Hsiao et al., 1996), is correlated with age-related decline in performance in delayed spatial alternation tasks. This decline in task performance was statistically correlated with decline in LTP, as assessed in both *in vivo* and *in vitro* studies (Chapman et al., 1999). Such correlations are rarely expected, because they reflect a statistical correlation approach, more than a mechanistic connection (Martin et al., 2000). Although the AAP transgenic models have been used for such studies, there is a huge gap in the understanding of the function of the beta amyloid protein yet to be linked to the mechanisms of induction and expression of LTP (Seabrrok & Rosahl, 1998). Although some studies have demonstrated that in APP knockout mice, an impairment of task performance (factors that contributed to the altered watermaze performance in mutants were, considered as alteration in swim speed, thigmotaxis, and alteration of spatial memory) was clearly observed, no difference was observed between groups where LTP was induced. Once that such factors were removed from mutants, after a careful behavioral analysis, a clear correlation in the magnitude of induction and expression of LTP between mutants and controls was obtained, thus LTP correlated with third factor, that is, spatial memory (Lipp & Wolfer, 1998).

Successive episodes of LTP may have a cumulative effect at least in population of neurons (Petersen et al., 1998), but this does not implicate that saturation of plasticity is available in the neural pathway being stimulated (Jeffrey, 1997). Therefore, cumulative LTP should be able to enhance neural throughput, improving learning as in a reflex neural system (Martin

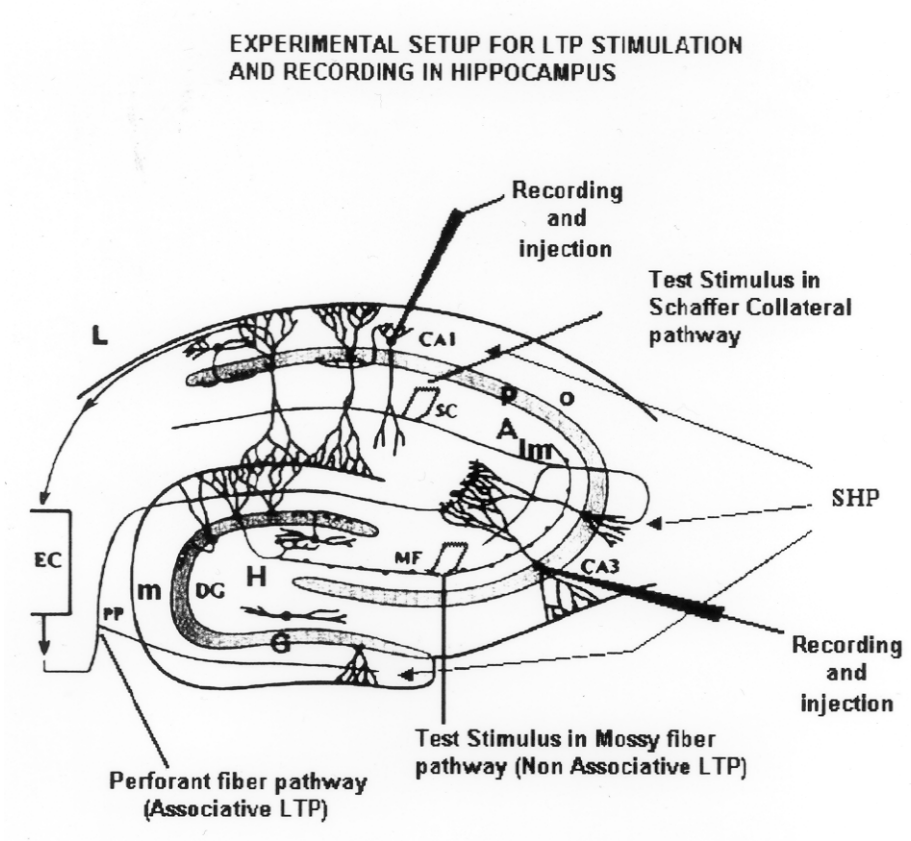

Fig. 3. Schematic representation of the experimental set up for studying Long-term potentiation (LTP) in CA1 and CA3 regions of the rat hippocampus. Stimulating electrodes are placed either in different local neural pathways so as to activate independent neural circuits to the CA3 or CA1 pyramidal neurons. Thus, both the Schaffer collateral pathway (SC) or the Mossy fiber pathway (MF) might be electrically stimulated with tetanic train stimuli (test stimulus of 1 or 4 trains of 100 Hz/1s every 60 sec) to elicit electrical responses recorded in the CA1 or CA3 pyramidal cell region, respectively. Other hippocampal areas and fibers (such as commissural pathway from CA3 region of contralateral hippocampus or ipsilateral perforant fiber pathway) can be electrically stimulated to obtained cell responses of enhancement of EPSPs and the resultant slope increases of EPSPs as a measure of synaptic efficacy, reflecting the induction of the early and late LTP phenomena. (Figure adapted from Ascoli et al., 1998; Kandel et al., 2000, and modified by author of the present publication). (For details and information of figure, see figure 1, section IIIa, Leff et al, 2002).

et al., 2000). Conversely, saturation of LTP prior to behavioral training should be able to prevent new learning because further LTP induction, or applied to LTD, would be impossible.

Saturation, being poorly defined, has been conceived as a state in which each synapse on a particular neural pathway has been potentiated to a maximal level, so that the probability of transmitter release at every pre-synaptic terminal and the post-synaptic receptor efficacy have reached *ad maximum* (Martin et al., 2000). Nevertheless, physiologically, this definition, would put a neural network in a state of seizure activity. Thus, an alternative postulate to define saturation should be used: It should be defined as a neural state in which, for a certain period of time, no further LTP induction is possible (Martin et al., 2000). In such context, initial studies concerning the behavioral effects of LTP saturation demonstrated that saturation was able to induce a reversible occlusion of subsequent spatial learning (Castro et al., 1989; Cain et al., 1993; Jeffrey & Morris, 1993; Korol et al., 1993; Sutherland et al., 1993). Although no further replication of these earlier findings was demonstrated, replica of same studies revealed that no learning deficit could be observed. In an attempt to explain a number of inconsistencies, several studies were designed to maximally activate the perforant path, under different experimental conditions, and demonstrated that experimental groups of animals, receiving high-frequency trains (saturated subgroup) which were unable to induce further LTP, failed to learn the watermaze task as compared to controls (that received low-frequency stimulation) who learned to locate the platform after training sessions on a watermaze task (Moser et al., 1998; Mumby et al., 1993). These set of results demonstrated that saturation of LTP in the PP (figure 3) does impair spatial learning as previously claimed by McNaughton et al. (1986) and Castro et al. (1989). Moreover, several reports still remain skeptical regarding these positive findings. In these reports authors argued that repeated tetanization may induce an acute pathological state, producing seizure-like responses after discharges, which might result in learning deficit (McEarning & Shaw, 1996). Although those observations were not found in such previous experiments, animals with LTP saturation showed an impairment of task performance, besides that all animals received same course of tetanic stimulation (Martin et al., 2000). Although experimental LTP saturation may be successful, it is still argued that compensatory changes (e.g., alteration of the functional inhibitory transmission, synapse formation, and a reduction in post-synaptic sensitivity) may be the cause for learning impairment, rather than LTP saturation. LTP saturation might cause an increase in synaptic inputs, therefore an increase in the efficacy of synaptic transmission would be able to disrupt physiological hippocampal information processing (see Moser & Moser, 1999 and Martin et al., 2000, for more details). Besides these controversial issues, several studies demonstrating normal learning, despite LTP induction, implicate that increases in synaptic weights do not alter the encoding of new information, and several experimental evidences showed no correlation between the magnitude of LTP induced by cross-neural pathway tetanization (Moser et al., 1998 for precise details) and further learning (Martin et al., 2000). Further studies are needed to confirm such observations, employing pharmacological approaches that could be able to induce and observe discrete changes in the onset of the synaptic potentiation (Martin et al., 2000).

PHARMACOLOGICAL STUDIES ON LTP: IMPLICATIONS TO LEARNING AND MEMORY

Several behavioral studies focused in LTP and on learning and memory have conducted pharmacological approaches using several NMDA glutamate receptor antagonists. Since the original observations conducted by Morris et al. (1986), who demonstrated that the NMDA receptor antagonist AP5 was able to block spatial discrimination learning, several works have shown that competitive NMDA antagonists impair hippocampal formation-dependent learning based on different learning paradigms and operant tasks (see Martin et al.,2000, for detailed information). Such hippocampus-dependent impairment has been shown to follow a dose-dependent fashion over a range of intrahippocampal drug concentrations that also impair *in vivo* and *in vitro* hippocampal LTP (Davis et al., 1992). Although these pharmacological approaches strongly support the SPM hypothesis as detailed above, several pharmacological parameters have to be taken into account when using receptor antagonists to impair or enhance LTP processing and memory as well (Martin et al, 2000). For instance, drug diffusion is important when considering the pharmacological method of infusing NMDA antagonist. In several laboratories, the ICV administration method for selectively infusing NMDA antagonists, such as AP5, results in drug diffusion to different areas of the brain (forebrain) (Butcher et al., 1991). Thus, ICV administration including IP injections of different concentration range of NMDA antagonists, will likely block several forebrain-dependent learning processing known to mediate sensorimotor, cognitive and hippocampal-

NMDA receptor-learning processes. Such situation has been demonstrated after local injection of nanomolar concentrations of AP5 into the dorsal hippocampus, resulting in a spatial learning impairment in watermaze paradigms (Morris et al., 1989; Martin et al., 2000). Diffusion of antagonists and global NMDA-receptor antagonism will produce several sensorimotor disturbances in several operant-performing tasks (Cain et al., 1996; Saucier et al., 1996). Such abnormalities could result in the diffusion of drugs from ventricles to the thalamus, disrupting both somatosensory and visual information, or in diffusion to the striatum, producing motor disturbances (e.g., flaccidity)(Sillito et al., 1985; Salt & Eaton, 1989; Turski et al., 1990). When visual, somatosensory and motor transmission is altered, learning will be difficult to proceed (Martin et al., 2000). Moreover, several reports have documented that administration of non-competitive NMDA-receptor antagonists such as MK-801 produce sensory inattention and motor stereotypies (Koek et al., 1988; Keith & Rudy, 1990; Tiedke et al., 1990; Danysz et al., 1995; Cain et al., 1996) as occurs with local infusion of high doses of AP5, doses substantially high, needed to block LTP *in vivo* (Martin et al., 2000). Some studies have shown that impairment of spatial learning in operant performing tasks is correlated with sensorimotor disturbances (Cain et al., 1996; see Martin et al., 2000 for details), but other have demonstrated that such learning impairment, occurring normally after IP injection of NMDA antagonist, disappears if animals are pretrained to prevent drug induced sensorimotor disturbances in naïve animals. Pretrained animals, showing LTP blockade, show no sensorimotor disturbances and normal spatial learning tasks (e.g., watermaze) (Saucier & Cain, 1995; Bannerman et al., 1995). Although some studies, have found that NMDA antagonists induce impairment in spatial learning (depending on the performing task, animals are exposed and the observations obtained) some concepts have been given to explain sensorimotor disturbances, such as: blocking NMDA receptors induce dissociation of different components of spatial learning; impairing animal's ability to learn a required strategy but not the orientation where operant task is situated (Bannerman et al., 1995). In the same context, others have reported using same task strategy, in freely moving animals trated with an i.p. injection of the NMDA receptor antagonist CGS-19755, with a dose sufficient to block LTP, in CA1 region and dentate gyrus, learned both non-spatial strategies and developed normal performance of spatial learning tasks and spatial reversal to controls (Hoh et al., 1999). Thus, animals can learn several qualitatively different forms in any given task and dissociable components of spatial learning can be disclosed depending on the complexity of the tasks and protocols (Martin et al., 2000).

Different electrophysiological studies have been conducted in order to observe the effects of the NMDA antagonists (e.g., CPP, AP5) on hippocampal place fields. These studies have revealed that after drug infusion the previous firing fields remain unchanged and exposing animals (rats) to new environment allows the normal acquirement of previous place fields which result to be unstable over time (Kentros et al., 1998). Although the temporal instability could complement the findings of different reports, documenting that poor learning in naïve animals occurs when these are exposed to one single trial per day (Bannerman et al., 1995), but not in spatially pretrained animals treated with AP5, who learned well in novel environments (Martin et al., 2000). Animals infused with AP5 show no effect on performance at short memory delay (i. e., 15 sec intertrial interval) in finding a hidden platform in watermaze task, whereas control animals show long escape latencies on the first trial and shorter latencies on subsequent trials, when they know where platform is located. Experimental treated groups exhibit a pronounced impairment during the first 20 min and 2 h after as compared to controls. This delay effect or delay-dependent deficit occurs irrespectively, either if animals stay in training context, or if they are subsequently returned to the normal housing, or regardlessly of the route (ICV *versus* intra-hippocampal), and time period of administration of the drug (chronic *versus* acute, respectively). Thus, this set of results shows that delay dependent memory impairment, independently of their cause, either by sensorimotor disturbance or in an attention deficit in nature, temporal instability of place fields occurs only when novel contexts are present (Martin et al., 2000). Moreover, after NMDA receptor antagonist blockade at the hippocampus, AMPA receptor should be free mediate receptor-dependent fast transmission. Under the possibility that such antagonist agents could alter the spatial distribution of synaptic inputs or weights throughout the hippocampal formation, circuitry is quite obvious, but even under such situation, network neurons should be able to fire while transmitting information (Martin et al., 2000). Thus, in such context, NMDA antagonists may be capable of impairing the encoding of memory traces with no effect on memory retrieval, as shown in animals treated with NMDA antagonist-AP5. After being trained in odor discrimination, learning has no effect on retention, but it eventually impairs new learning tasks (Staübli et al, 1989). Furthermore, AP5 has no effect on retention in watermaze performing task, while lesions to hippocampus disrupt retention when applied shortly

after the end of training, as demonstrated by entorhinal cortex lesions which cause a fast forgetting on olfactory information (Morris, 1989; Morris et al., 1990).

Assuming that NMDA receptor-antagonists in the hippocampus are able to disrupt memory and storage, it could still be considered that such event is unrelated to LTP. Low doses of NMDA receptor antagonists, although too low to block LTP *in vivo*, have been shown to enhance learning tasks such as social learning and step-down inhibitory avoidance (Mondadori et al., 1989; Lederer et al., 1993), such antagonist-induced facilitation of learning presumably would be mediated through different mechanisms other than activation of NMDA-receptor dependent form of LTP. Different studies, using therapeutic doses of the noncompetitive antagonist, memantine, have demonstrated to impair neither learning nor LTP. This mechanism may be due to its rapid on and off-channel blocking kinetics, but due to its neurotoxicity effects and dose-effect limitations, memantine could work preventing impairments in cognitive function (Parsons et al., 1999). Moreover, NMDA currents contribute to normal synaptic transmission at several neural transmission systems such as somatosensory and visual relays in the thalamus (Salt & Eaton, 1989; Sillito et al., 1990), as well as in the lamprey spinal cord, where studies have revealed to be involved in modulating the rhythmical neuronal repolarization, turning on Ca^{2+}-dependent K^+ currents (Grillner et al., 1990). Under such context, it has been shown that acute ICV infusions of AP5 disrupt theta rhythm and decrease population spike amplitude in the hippocampus (Desborough, 1988; Abraham & Mason, 1988). Thus, synaptic transmissions based on NMDA currents have much more implications in neuronal functions other than just plasticity itself (Martin et al., 2000). In order to delineate how NMDA receptor antagonists affect several neural transmission systems during conducting behavioral studies, several works have focused in the use of alternate novel drugs, capable of interacting with the NMDA receptor complex at different binding sites, or acting selectively with the metabotropic NMDA receptor as well (see figures 3 and 4 on previous chapter), or even, employing intervening drugs, acting downstream the NMDA receptor, at the intracellular signaling pathways, or specifically using a complementary approach such as gene-targeting strategies. Thus, such compounds might help in a certain way, to elucidate how NMDA-mediated processes are affected, leaving ones intact, while still blocking LTP (Martin et al., 2000).

Both *in vitro* and *in vivo* experiments using mGluR antagonists such as the alpha-methyl-4-carboxyphenyl-glycine (MCPG) have shown that this compound was able to block LTP leaving STP unaffected (Bashir et al., 1993; Riedel et al., 1995). Thus, the pharmacological action of such antagonists should be quite different from the induced effects of AP5, causing a sensitivity effect in memory delay. Nevertheless, such results have raised several questions regarding the blocking LTP effect of the antagonist, due that LTP blocks it under specific circumstances, both *in vivo* and *in vitro*, in hippocampal slices (see Martin et al., 2000, for precise details). Moreover, the mGLuR subtype itself has not clearly demonstrated its implications in LTP (Breakwell et al., 1998; Fitzjohn et al., 1998). Nevertheless, both MCPG and other selective drugs (e.g., AIDA) have been reported to alter normal spatial learning and contextual fear conditioning in rodents (Richter-Levin et al., 1994; Riedel et al., 1994; Bordi et al., 1996; Nielsen et al., 1997) making no observations on memory varying delay on tasks under drug action (Martin et al., 2000).

Several pharmacological works have demonstrated that agents that interfere with the synthesis of nitric oxide (NO) induce impairments in both spatial learning and olfactory recognition (Chapman et al., 1992; Hölscher et al., 1996; Kendrick et al., 1997). These findings have been disputed because there is no information implicating NO in LTP yet (Hawkins et al., 1998), and no clear indication exists of whether alterations in behavioral performance occurring in the presence of different NOS inhibitors, are acting directly on the CNS or independently, as a consequence of inhibiting endothelial NOS (Bannerman et al., 1994). Thus, it might be possible to elucidate such controversial issues, using neuronal NOS inhibitors, such as 7-nitro-indazole, as it has been demonstrated that it impairs spatial learning at doses that block LTP in the CA1 area of the hippocampal formation *in vivo* (Hölscher et al., 1996).

Thus, overwhelming compelling evidence indicate that blockade of hippocampal NMDA receptors during learning, disrupts the acquisition of the hippocampal dependent forms of memory. Moreover, these results support not only the SPM hypothesis (described above) but furthermore, they support the idea that NMDA receptor-dependent plasticity is relevant for memory processing (i.e., encoding memory), but not for the retrieval of memory (Martin et al., 2000). Although the SPM hypothesis does not predict that drugs that necessarily enhance LTP will enhance memory, novel drugs such as ampakines (by means of decreasing the rate of desensitization of AMPA receptor, enhancing a slow time course in the deactivation of receptor currents after agonist application (Arai et al., 1994, 1996) including benzodiazepine inverse agonists (Seabrook et al., 1997; Fontana et al., 1997; Letty et

al., 1997) have been shown to facilitate LTP as well as to enhance the encoding of memory in several performing tasks as several studies have revealed (Lynch et al., 1998).

SHORT-TERM PLASTICITY AS GENERATOR OF TEMPORAL FILTERS FOR INFORMATION PROCESSING

Short-term plasticity has been defined as the activity dependent decrease (depression) or increase (facilitation) in synaptic transmission occurring within hundred of milliseconds of the onset of specific temporal patterns of activity (Zucker, 1989; Zucker, 1999; Fortune and Rose, 2000). Most rapid changes in synaptic strength (depression and facilitation) result from pre-synaptic activity with small contribution of post-synaptic desensitization (Jones & Westbrook, 1996; Otis et al., 1996). While these synaptic plasticity events have been linked at the functional level to behavioral habituation and sensitization, respectively (Zucker, 1989; Stofer & Carew, 1996; Fisher et al., 1997; see also previous reviews in Leff et al., 2001b) several studies have shown that neural circuits displaying short-term plasticity are ubiquitous in the brain of mammals as well as in the brains of non-mammalian species. Moreover, novel hypothesis have been recently proposed, postulating that both short-term depression and facilitation contributes to generation of filtering functions that are relevant for information processing. Therefore, this hypothesis proposed that short-term plasticity might be functionally relevant for processing several complex forms of learning and memory, besides its role in simple forms of learning (Fortune & Rose, 1999). Based on such context, electrophysiological studies have demonstrated that many sensory neurons in the brain of mammals as well as sensory systems of invertebrate species and electrosensory midbrains of some fish, respond strongly to low-frequency stimuli (< 10 Hz) and weakly to high-temporal frequency stimuli (> 10 Hz)(Rose & Fortune, 1999; Chance et al., 1998; Varela et al., 1997; Haag & Borst, 1996). Data analyzed from intracellular recordings and based on recent computational models led to the hypothetical proposition that synaptic short-term depression activity contributes to low-pass temporal filtering (Fortune and Rose, 2000; Chance et al., 1998; Varela et al., 1997), in such a way that response to sensory transients or patterns of cellular activity resulting from slow changes (< 10 Hz) in signal amplitude are passed, whereas fast repetitive patterns are rejected as based on the neural correlates of the behavioral response of the weakly electric fish (Fortune & Rose, 2001). These fish see their environment through a temporal filter in such a way that they adjust their electric organ-discharge frequencies by rejecting interference signals caused by interactions of the electric field of neighboring fish, at rates over 10 Hz. Thus, these species have naturally adapted to locate objects in their surroundings by means of their electric sense, despite the on-going background/high-frequency interference (Matsubara & Hellingenberg, 1978). This set of results led to the proposition that synaptic depression might be one of the main mechanisms for generating and regulating low-pass temporal filters (see Fortune & Rose, 2001, for extended details). Such proposed neurobiological mechanism has been better understood by analysis of the intracellular recordings of the midbrain neurons of these electric fish. These studies have shown that both passive and active membrane properties contribute to such low-pass temporal filter (Fortune & Rose, 1997), demonstrating that declines in PSP amplitudes (postsynaptic potentials) as a result of homosynaptic short-term depression, increase low-pass filtering (Fortune & Rose, 2000, 2001). The relevance of short-term depression as a widespread and predominant mechanism that occurs in independently evolved sensory systems, enhancing the synaptic plasticity of several sensory responses in the brain of mammals, is still a controversial issue, but one hypothesis explaining the significance of such neurobiological mechanism employed to allow low-pass temporal filtering in sensory systems has been proposed: this form of plasticity might serve a common functional role in each of the neural circuits expressing such activity. Thus, activation of short-term synaptic depression used for low pass-filtering, which paradoxically, is induced by continuous high-temporal frequency stimuli, could be functionally relevant for preventing neural responses to low frequency information. Conversely, activation of short-term synaptic facilitation could be physiologically relevant to maintain responses to low-temporal frequency information (Fortune & Rose, 2001). Overall, short-term synaptic plasticity might be essential for spatio-temporal processing in the nervous system of mammals.

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