ACTUALIZACION POR TEMAS

SYNAPTIC PLASTICITY: UNDERSTANDING THE NEUROBIOLOGICAL MECHANISMS OF LEARNING AND MEMORY. PART I

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SUMMARY

Plasticity of the nervous system has been related to learning and memory processing as early as the beginning of the century; although, remotely, brain plasticity in relation to behavior has been connoted over the past two centuries. However, four decades ago, several evidences have shown that experience and training induce neural changes, showing that major neuroanatomical, neurochemical as well as molecular changes are required for the establishment of a long-term memory process. Early experimental procedures showed that differential experience, training and/or informal experience could produce altered quantified changes in the brain of mammals. Moreover, neuropsychologists have emphasized that different memories could be localized in separate cortical areas of the brain, but updated evidences assert that memory systems are specifically distributed in exclusive neural networks in the cortex. For instance, the same cortical systems that lead us to perceive and move in our environment, are used as neural substrates for memory retrieval. Such memories are the result of the repeated activity of millions of neurons assembled into distinct neural networks, where plastic changes in synaptic function leads to the strengthening of the same synaptic connections with the result of reconstructed permanent traces that lead to remembrance (Hebb Postulate). Elementary forms of learning and memory have been studied in simple neural systems of invertebrates, and as such have led the way for understanding much of the electrophysiological and neurochemical events occurring during LTP. Long-term potentiation (LTP) is the result of the increase in the strength of synaptic transmission, lasting as long as can be measured from hours to days. LTP has been detected in several areas of the brain, particularly, in the hippocampus, amygdala, and cortex, including several related limbic structures in the mammalian brain. LTP represents up to date the best model available for understanding the cellular basis of learning and memory in the central nervous system of mammals including humans.

Key words: Brain plasticity, synapses, learning, memory, long-term potentiation, experience, training.

RESUMEN

Uno de los fenómenos más interesantes dentro del campo de la neurobiología, es el fenómeno de la plasticidad cerebral relacionada con los eventos de aprendizaje y el procesamiento del fenómeno de memoria. De hecho, estos fenómenos neurobiológicos empezaron a ser estudiados desde principios de siglo. Remotamente, el fenómeno de plasticidad cerebral en relación con el desarrollo y aprendizaje de las conductas fue ya concebido y cuestionado desde hace más de dos centurias. Sin embargo, desde hace cuatro décadas, múltiples evidencias experimentales han demostrado que tanto la experiencia o el entrenamiento en la ejecución de tareas operantes aprendidas, inducen cambios plásticos en la fisiología neuronal, incluyendo los cambios neuroquímicos y moleculares que se requieren para consolidar una memoria a largo plazo. Asimismo, diversos procedimientos experimentales han demostrado que la experiencia diferencial, el entrenamiento y el aprendizaje de conductas o la experiencia informal, producen cambios mensurables en el cerebro de los mamíferos. Más aún, la neuropsicología ha considerado desde hace varias décadas que diferentes tipos de memoria pueden ser localizados en diferentes circuitos neuronales en distintas áreas de la corteza cerebral. Sin embargo, los estudios recientes han demostrado que los sistemas de memoria están distribuidos en circuitos neuronales corticales específicos. Por ejemplo, los mismos sistemas corticales que procesan la percepción sensorial y la función motora, son los mismos sustratos neurales que se emplean para procesar los fenómenos de memorización. El fenómeno de la memoria y el aprendizaje es resultado de la actividad fisiológica repetitiva de millones de neuronas que, ensambladas en circuitos neuronales específicos, conllevan al reforzamiento de las conexiones sinápticas involucradas y a los cambios de plasticidad sináptica que se requieren para establecer estos fenómenos neurobiológicos. El fenómeno de potenciación a largo plazo, o LTP, es un evento neurofisiológico que resulta del incremento en el reforzamiento de la transmisión sináptica, que puede perdurar en las regiones cerebrales estudiadas desde horas a días. El modelo de LTP quizá representa el modelo funcional experimental más viable para entender las bases celulares del aprendizaje y la memoria en el SNC de los mamíferos, incluyendo el cerebro de los humanos.

Palabras clave: Plasticidad cerebral, sinapsis, aprendizaje, memoria, potenciación a largo plazo, experiencia, entrenamiento.

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INTRODUCTION

Learning is the process by which we acquire knowledge and memory is the process by which we retain that knowledge over time (Kandel, 2000). The nervous system is capable to store information about oneself and ones environment. Almost all areas of the brain are involved in some kind of storing memory. For instance, in primates memory of past experiences is stored at most in the neocortex, a phylogenetical structure representing the newest part of the cerebral cortex. Most of the memory functioning in the brain is based on the availability of interconnected neural networks established along neocortical neurons. Neural substrate of memory and learning processes could be viewed as the upward expansion of hierarchy of neural structures in mammals, starting from less complex structures such as the spinal cord (Fuster, 1997). Every stage of that hierarchy is devoted primarily, if not exclusively, to basic functions such as sensing and acting, including the neocortex that contains a posterior sensory region as well as a frontal motor one (Fuster, 1997). Along the large experimental work, it has been established that different neural systems are involved in different types of learning and memory. Although neuroscientists distinguish between declarative or explicit, and non declarative or implicit memory, the vast majority of the memory processes that take place in non human animals including several aspects of memory in humans, are largely implicit. Implicit memories include forms of learning processes, namely, sensitization (non associative learning), basic associative learning and priming (Beggs et al., 1999) that ultimately are stored as forms of memory. Neural networks that underlie such learning processes (or defined as elementary forms of learning) have been recognized; for instance, non associative learning processes are mainly performed as reflex pathways and occupies neural circuits of the spinal cord; associative learning, which involves emotional responses and motor activities, are mainly and respectively processed in limbic structures such as the amygdala and in structures regulating motor activity such as the cerebellum. Priming (defined as the increased ability to identify or detect a stimulus as a result of prior exposure) occurs mainly at neocortical regions (Beggs et al., 1999). According to Hebb's postulates, if signaling between neurons takes place at synapses, then changes in signal strength could alter the low of activity within the brain and as a consequence, influence the way an organism responds to experience. Therefore it can be assumed that learning is the product of synaptic changes, as Hebb (1949) previously argued, "that learning involved coincident synaptic activation of neurons" (defined as Hebb synapse).

Much of the understanding about the cellular and molecular mechanisms underlying learning and memory come from the extensive research performed in both vertebrates and invertebrates neural systems from where several principles have been established (Byrne, 1987; Byrne et al., 1990; Byrne & Kandel, 1996): Multiple memory systems are processed by neural networks in the brain; short term forms of learning and memory require changes in preexisting neural circuits; thus, changes in local neurons relating with one or multiple forms of learning and memory, involve the activity of multiple cellular mechanisms (as will be exposed later) and those neurochemical events that mediate cellular changes, involve the activity of second-messenger systems, including changes in the properties of membrane channels. While short-term memory requires neural changes of preexisting cellular mechanisms, the establishment of long-term memory, new protein synthesis and growth has to occur as a main cellular event. There, long-term memory implies the existence of complex plastic changes occurring in activated synapses and specific neural circuits and therefore, those particular neurons that operate within them. Thus, finally, as a result of the plastic changes occurring in those neural networks involved in learning and memory processing, the brain will respond with increased ability and detect and identify those stimuli present in the animal's environment.

William James exposed more than a century ago in his "law of neural habit" (James, 1890, p.226): "*When two elementary brain processes have been active together or in immediate succession, one of them, on reoccurring, tends to propagate its excitement to the other*". Although he never specified the locus of the physiological modifications where associations form; he anticipate that the coactivity of elementary brain processes (contiguity) is a condition for the formation of associations within the brain (James, 1890).

The role of the activity dependent synaptic plasticity in the brain processes of learning and memory is one the most interesting issues in neuroscience. Most of the experimental work performed in this research field has been focused on the role of long-term potentiation (LTP) in learning. At the neurochemical and molecular level major studies have been centered on the glutamate transmission and the N-methyl-aspartate receptor–dependents form of LTP. One central question that has aimed the research of learning and memory is based on the idea of whether LTP equals memory (Edwards, 1995; Sossin, 1996).

As such, several attempts have been intended to categorize the types of LTP occurring in the brain, and in a similar track, which properties of the LTP are really relevant to memory formation, and this include

another facet of LTP, namely, long-term depression (LTD) or depotentiation. Moreover, questions have been raised concerning what types of learning are involved in the brain, and if such, are they specific to certain brain areas? Or as a general hallmark is LTP relevant to encoding, storage, consolidation and retrieval of memory processes. Several works regarding the putative role of LTP in memory formation have recently been focused on several demonstrations about the activity dependent synaptic plasticity and the multiple forms of memory that are known to exist in the mammals brain. Synaptic plasticity and memory, defined as SPM, independently of where they occur in different areas of the brain, share common features: Activity dependent synaptic plasticity is induced at appropriate synapses during memory formation, and this neural process is a prerequisite for information storage that underlies the type of memory mediated in the brain area where neuronal plasticity is observed (Martinez and Derrick, 1996).

Much of the clues of how the brain encodes memory as a biological entity come from the brain's cellular architecture. In fact, in the mammalian brain, millions of neurons interconnect in vast neural networks throu billions of synapses. Thus, it can be assume from such biological fact, that a single neuron is unlikely to encode for a specific type of memory, rather the participation of ensembles of neurons is the result that maintains a representation of a certain kind of memory. Dynamic interactions among neurons and the capability of modifying such interactions mean that, use-dependent changes in synaptic functions are required for memory processing and storage (Martinez and Derrick, 1996). The fact that we understand that memory is stored through changes via synaptic function, the experimental evaluation to assert this theory, comes from previous information that Hebb (1949) already postulated: Memories are represented by reverberating assemblies of neurons. He recognized that a memory representation cannot reverberate forever, and thus a need for some alteration in the neural circuit specifying for such memory is required, as to provide integrity and make the neuronal assembly a permanent trace that can be afterwards reconstructed as a remembrance (Hebb, 1949). Thus, the activity of such neural network dependends on altered changes in the synaptic function (synaptic plasticity) as formalized by Hebb postulate: "When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A´s efficiency, as one of the cells firing B, is increased" (Hebb, 1949). This postulate enunciation has been experimentally demonstrated 30 years later, by

the definition of long-term potentiation (LTP), where LTP seems to operate in neural networks to store memory in a manner similar to the one Hebb postulated (Martinez and Derrick, 1996). LTP, as first reported by Bliss and Lomo (1973), is a cellular model of synaptic plasticity occurring in the brain of vertebrates (Sossin, 1996) and found to occur in several areas of the neocortex (Bear & Kirkwood, 1993), in the hippocampus (Bliss & Lomo, 1973; Marr, 1971) and in the amygdala (Maren, 1999). In all of the areas studied, a trace of neuronal activity has been established as a result of the strengthening of synaptic connections. Thus, from Hebb´s postulate to the discovery of LTP, it has been established that the theoretical connections among neurons are strengthen as a result of altered changes in synaptic activity, thus inducing long lasting changes in the synaptic connections: the Hebbian Synapses (Martinez and Derrick, 1996). Thus, the Hebbian postulate has led to the assertion that a memory network in the brain (Fuster, 1997) can efficiently storage a number of memory representations within a same neural network (McNaughton & Morris, 1987). Moreover, one final assertion about memory is that if memory is stored in networks of neurons and if the efficiency of this network is thus mediated by persistent activity (Hebb's postulate), LTP induced by persistent stimulation (tetanic stimulation; Bliss & Lomo, 1973) of an afferent pathway is at least one of the possible physiological mechanism by which brain stores information (Martinez and Derrick, 1996). Thus, LTP can be postulated to be a substrate of the memory, as we shall explain in the next section.

HISTORICAL BACKGROUNDS

The first explanations on the mechanisms linked in the process of memory were initiated itself with Aristotle who mentions "Acts of recollection, as they occur in experience, are due to the fact that one thought has by nature another that succeeds it in regular order" (Yates, 1966). Further speculations about the brain regions involved in learning were discussed as early as 1783, regarding the possibility of testing whether mental exercise can induce the growth of the brain (Bonnet, 1779-1783). This hypothesis was explored by several neuroanatomists who demonstrated that after a long training period in mammals and birds, certain areas of the neural tissue, such as the cerebellum, increased in size and folds [Malacarne, in J. de Physique(Paris) 43:73,1793]. Thus, besides that two main doctrines (phrenology and evolution) emerged in the 19th Century supporting the idea that exercise or training can enlarge particular brain regions through inheritance of acquired

characteristics (Rosenzweig, 1996). As such, Gall emphasized that the innate development of different "organs" of the cerebral cortex, corresponded to different mental faculty, and such capabilities are determined innately. Moreover, Gall argued that exercise or training influence the development of innate faculties or the "organs" of the brain (Gall, 1819) as opposed to Lamarck, who rejected Gall´s hypothesis, mentioning that the brain and other special neural regions develop through appropriate use of related faculties (Lamarck, 1809). Besides, the phrenologist movement, supporting that faculties of the cerebral organs could be developed by training (Spurzheim, 1815, 1847), several accumulated evidences at the end of the 19th Century, showing that the brain suffer less individual variations in size with respect to other organs, when body weight comes into account. Thus, it was established in consensus, that the gross anatomy of the brain was not affected by experience or training, that the adult brain is essentially fixed anatomically (Rosenzweig, 1996).

Several scientists, started to speculate that changes in neural junctions, might putatively account for the occurring of memory process, as suggested by Bain (1872) who reported that memory formation involves a "….specific growth in the cell junctions" or more recently what we denominate synaptic junctions (Finger, 1994). Furthermore, William James (1890) was not only the first to point out the attribute of the plastic properties of the nervous system or to describe " about molecules storing habits in the nerve cells" (James, 1890). Centuries before, practices to improve memory were codified in what became known as the art of memory (Yates, 1966). The neuron doctrine advanced such speculations and hypothesis, making reference that plastic changes involved in learning might take place at the junctions between neurons (Tanzi, 1893). Eighty years later elapsed before demonstrating the first results of such announcement: that development and training induce plastic changes in the synaptic junctions (Cragg, 1967; Diamond et al., 1975; Globus et al., 1973). This initial hypothesis, was explored by the Spanish neuroanatomist, Ramón y Cajal, who stated that "the higher one looked in the vertebrate scale, the more neural terminals and collaterals are ramified", and the fact "that neurite branches increased during brain development up to the adulthood, make feasible that mental exercise leads to increase growth of neural branches" (Ramón y Cajal, 1894). Ramón y Cajal «assumes that the volume of the brain can remain constant even when a great neural branching and "formation of new terminals of the neurons" are present, at the expense of a reciprocal diminution of the cell bodies and /or shrinkage of other brain areas,

whose function is not directly related to intelligence» (Ramón y Cajal, 1894). These neural junctions specified independently by Tanzi and Ramon y Cajal, had no specific name, and the name connoted as "synapse" years later by the famous neurphysiologist Charles Sherrington, would become the focus of interest of neurobiologists, as Sherrington stated that synapses were likely to be strategic for learning (Sherrington, 1897). Based on these findings, psychologists and several researchers during the first half of the 20th Century, proposed the hypothesis that memory would involve either the growth of neural fibrils toward one another in order to narrow the synaptic gap, or subtle chemical changes at synapses would occur for memory storage (Finger, 1994) (not very far away to what has been demonstrated for LTP as experimental model for long-term memory). However, several evidences at the mid 20´s, concluded no solid evidence to support such "growth" theories (Lashley, 1950). As such, Lashley (first author to recognize the futility of trying to localize memory) offered several criticisms: Neural cell growth is too slow to account for the rapidity with which some learning occurs, and therefore, there's no warrant to look for localized changes (Lashley, 1950). Despite Lashley´s refutation of the growth theories on memory formation, some evidence for neural changes occurring at synapses were noted by Hebb (1949), reviving the previous hypothesis that memory formation could imply conditions that would lead to new synaptic junctions, and the research concerning the properties of such synapses has been defined as Hebbian synapses (Rosenzweig, 1996).

TRAINING OR EXPERIENCE ALTERS THE NEUROCHEMISTRY AND THE ANATOMY OF THE BRAIN

Though the concepts of brain plasticity in relation to behavior started to clear just some few decades ago, whereby several evidences showed that training and experience produce neurochemical and neuroanatomical changes in the brain tissue, later demonstrated that such neural changes are required for long term-memory (Rosenzweig, 1996). The starting point of memory science could be dated as early as 1885, where clinical observations and experimental research, knew about the differentiation between declarative and non declarative kinds of memory, as neurological studies would evidence what type of memory are lost and what´s spared after certain kinds of brain damage (Wilks, 1864; Ribot, 1881). Such distinction was quite necessary in order to find the brain areas involved in these two kinds of memory, and thus, to distinguish the brain areas involved in different kinds of amnesia (Squire, 1993).

In the early 60´s two separate research works announced important findings showing that the brain can be altered quantitatively by either training or experience. Firstly, it was demonstrated that formal training and informal experience in distinct environments leads to pronounce changes in both the neurochemistry and neuroanatomy of the rodent brain (Rosenzweig, 1996). In parallel, other reports demonstrated that plastic changes in the cortex could be detected after depriving an eye of light in a young animal; this reduced the number of cortical cells that respond to subsequent stimulation of that eye (Hubel and Wiesel, 1965; Wiesel and Hubel, 1963; Wiesel and Hubel, 1965).

In such context, several experimental works demonstrated that the exposure of animals to long training and tested to solve difficult problems, resulted in a significant increase of AChE activity in the cortex in relation to animals trained to solve easier problems, or groups given no training and tested as well (Rosenzweig et al., 1961). Furthermore, besides the demonstration of the increase of cortical AChE activity occurred in animals (little mates) exposed to formal training (Rosenzweig et al., 1961), informal enriched environment also led to an increase of cortical AChE activity (Krech, 1960) and even more, to an increase in the weights of specific neocortical regions (Rosenzweig et al., 1962). Although this was the first evidence that training and differential experience could lead to structural changes in the brain (Bailey and Kandel, 1993), similar contextual experiments, using enriched environments, showed that even those small remarkable differences in weight could be estimated and detected and were specific to some neocortical areas. Thus, these results showed that invariably in almost all brains studied, the largest cortical area measured was the occipital cortex and the smallest were found adjacent to the somesthetic cortex, while extracortical regions showed very little or no significant changes (Bennett, 1964 a,b). Moreover, several findings supporting these result were reported, demonstrating that experience increased cortical thickness (Diamond et al., 1964), size of neuronal cell bodies and nuclei (Diamond, 1967), size of synaptic contacts (West & Greenough, 1972), number of dendritic spines versus length unit of basal dendrites (increase of 10%) (Globus et al., 1973), extent of dendritic branching (increase over 25%) (Holloway, 1966; Greenough & Volkmar, 1973), and increase in number of synapse per neuron (Turner & Greenough 1985). The latter was due mainly as a result of the increase of dendritic branching which causes neuronal cell bodies to be spaced farther apart in the neocortex of animals exposed to enriched conditions. These effects, translated into the substantial increase in cortical volume and intracortical connections, finally allows the upgrade processing capacity of the concerning cortical areas. Obviously, these results contradict previous speculations of Ramon y Cajal (1894) that training causes cell bodies to shrink in order to facilitate the growth of neural arborizations. Overall, these set of results demonstrated that enriched experience produces changes in specific cortical regions and not an unspecific growth throughout the brain, as early theories speculated (Rosenzweig, 1996). At the same extent, larger cell bodies are required to maintain the increased arborization, enhancing the increased cortical volume at the expense of the growth of cell bodies and dendrites (Rosenzweig, 1996).

Based on these set of results, different experimental works showed that differential experience actually produce dramatic effects in other parts of the brain that previously were known to be implicated in learning and memory formation, such as the cerebelar cortex (Pysh and Weiss, 1979) and hippocampal dentate gyrus (Juraska et al., 1985). Nevertheless, neurophysiologists, like Sir John Ecless (1965) believe that memory and learning storage involve "growth just of bigger and better synapses that are already there, not growth of new connections". But despite the several reports indicating that the number and size of synaptic connections increased as a result of training (learning), several authors agreed that both negative and positive synaptic changes were capable of storing memory (Rosenzweig et al., 1972). Such thesis is supported by several theoretical discussions that suggested that depending on the brain measured and upon the kind of training or exposure to differential experience, one may find an increased number of synaptic connections, increase in synaptic size, and either decrease in number or decrease in synaptic size (Rosenzweig et al., 1972, 1996).

Further experiments revealed that short periods of enriched or impoverished experience were sufficient to induce significant changes in the brain at any time during the life span of the organism (Rosenzweig, 1996). This contrasts with previous results from Hubel & Weisel (1965), who reported that eye occlusion altered cortical responses only when the eye was deprived during a critical period early in life. Further experiments reported parallel results: that modification of sensory experience in adult animals, such as touch and hearing, could disrupt receptive fields of cells as well as cortical maps for each modality (Kaas, 1991; Weinberger, 1995). Although it was assumed that plastic changes in the brain were more sensitive at early stages of life span, several experiments performed in selected animals, exposed to differential environments, demonstrated that irrespective to age or time exposure to enriched

environments (Zolman & Morimoto, 1962; Bennett et al., 1964a; Rosenzweig et al., 1963, 1968; Riege, 1971) the animal´s brain expressed clear effects either on measurable cortical weights (Bennett et al., 1970) and on dendritic branching (Kilman et al., 1988) or on altered cortical total mRNA concentration (Ferchmin & Eterovic, 1986). Therefore, if such results support that differential experience throughout life span, cause cerebral changes in a relatively rapid manner, this would be consistent with the fact that the effects are due to a learning process. This was based on early observations that formal training (learning) causes significant changes in cortical neurochemistry (Rosenzweig, 1996), and by several experimental evidences that showed that formal visual training confined to one eye of rats caused a significant increase in dendritic branching in the visual pathway contralateral to the open eye (Chang & Greenough, 1982). Following similar track of experimental work, recent reports have revealed that changes in density of dendritic spines occur after single formal training in chicks (trial-peck-avoidance) (Lowndes & Stewart, 1994). Though plastic changes occurring in the brain actually impinge on adults or older organisms, implying that a learning process has taken place; the effects induced by the experience of differential environment develop somehow more rapidly in younger than older animals, and similarly, the measurable effects are significantly more pronounced in younger animals.

Plastic changes in the brain, independently of the brain area or age of the effect-response, are known to be mediated by several transmission systems. For instance, infusion of acetylcholine or noradrenaline, can restore the plasticity of the adult visual cortex, after eye deprivation (Baer & Singer, 1986). Moreover, plastic responses occurring after occlusion of one eye in the kitten brain (visual cortex) depends on glutamate transmission, so that pharmacological treatment with specific antagonist of the NMDA receptor prevents such specific neural plastic changes (Kleinschmidt et al., 1987). Therefore it can be assumed in general, that plastic changes in the brain, induced as a response to particular environmental cues, will depend on the brain region affected, on the kind of experience learned, and also on treatments that may enhance or impair neuronal plasticity (Rosenzweig, 1996).

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