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MOLECULAR BASIS OF LEARNING IN THE HIPPOCAMPUS AND THE AMYGDALA

-review-

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ABSTRACT
The hippocampus and the amygdala are structures of mammalian brain both involved in memorizing. However, they are responsible for different types of memory: the hippocampus is involved in creating and storing declarative engrams and the amygdala is engaged in some of non-declarative learning. During memorization, changes of synapses appear and it is believed that they encode information. Long-Term Potentiation (LTP) and Long-Term Depression (LTD) are two processes which provide to these changes which are called synaptic plasticity. LTP strengthens connections between neurons and because of that it is traditionally linked with learning. LTD as an opposite state is usually treated as forgetting. However, there are some evidences that it is true only for few types of non-declarative engrams. More sophisticated learning (like declarative learning) requires cooperation of these processes. Review is focused on functions and detailed signaling pathways of processes of synaptic plasticity.
KEY WORDS: *synaptic plasticity, learning, Long-Term Potentiation, Long-Term Depression, Long-Term memory*

There are three types of memory: sensory, short-term and long-term (Atkinsons *et al.*, 1968). Sensory memory has big capacities and relates to sensory receptors. It lasts as long as information is transmitted further: to short-term memory. It can store engram consisted of 7±2 and stays few seconds (with a possibility to extend that time with active recalling) (Sperling *et al.,* 1960, Miller *et al,*.1956, Squire *et al.,* 2004). The last type is long-term memory with almost unlimited capacities and duration as long as whole life span. Long-term memory can also be divided further: by access of a consciousness to its engrams (stored information): declarative and non-declarative memory. They consist of subtypes and detailed division is shown on fig. 1 (Squire *et al.,* 2004).

There are many structures in brain involved in memorization but there are two especially well-studied: the hippocampus and the amygdala. The hippocampus is a symmetrical structure of medial temporal lobe, part of three-layered archicortex (MacLean *et al.,* 1990). It consists of dentate gyrus (DG), *Cornu Amonis* (CA1, CA2 and CA3) and subiculum (Van Strien *et al.,* 2009). Electrophysiological research and clinical observation of patients with selective lesions of temporal lobes have shown

that the hippocampus is necessary in some parts of memory processes (Rugg*et al.,* 2012, Scoville *et al.,* 1957). It has got a role not only in memorization but this is a structure where some of engrams are stored (O'Keefe *et al.,* 1976).

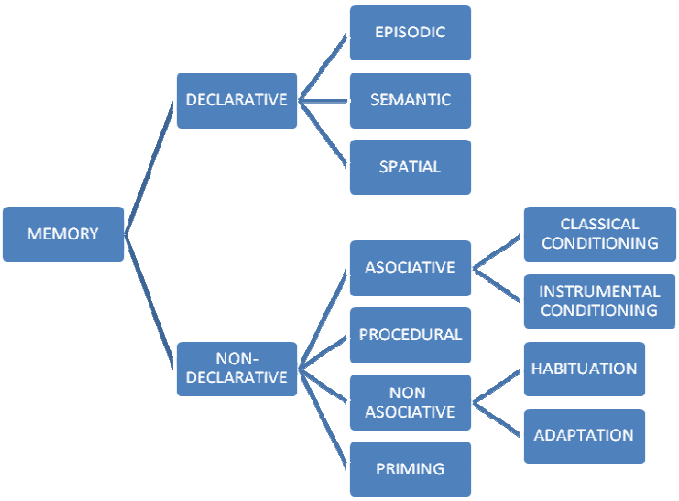

FIG.1. Division of long-term memory. Non-declarative memory is phylogenetically older and some of its types exist in simpler organisms like snail *Aplysia* (Castellucie*t al.,* 1970). Traditionally, declarative memory consists of episodic memory (information about personal experiences) and semantic memory (whole knowledge about the world). However, I want to add also spatial memory which can be consciously recalled. It is hard to say if non-primates (like rats) have episodic or semantic memory but it is well-reported that they have got a spatial memory (O'Keefe *et al.,* 1976). What is more they can not only navigate, but they seem to imagine they coming steps (Davidson *et al.,* 2009).

The amygdala is placed near the hippocampus but it has different anatomy. It consists of two parts: basolateral complex and cortically medial complex (with the cortical nucleus, the medial nucleus and the central nucleus) (Amunts *et al.,* 2005). The amygdala is responsible for emotional arousal which seems to enhance memorization (Kapp *et al.,* 1992).

The amygdala is also necessary to many types of non-declarative learning like classical conditioning (Goosens *et al.,* 2001). Because of the fact that medial part of the amygdala is a place where different brain pathways are crossing, some researchers claim that this is a structure of integration of conditioned (CS) and unconditioned stimulus (US) (Blair *et al.,* 2001, 2005). In research on rats it was shown that that conditioning learning is impaired in both situations of blocking the amygdala: before and after an experiment (Campeau *et al.,* 1995). So we can assume that this structure is involved not only in detection of stimuli coexistence but also in storage of some of engrams.

Synaptic plasticity is an adaptive value which is an ability of neural circuits to change its properties upon experiences (Citri *et al.,* 2008). Changes on neural level can be observed also during learning and they are are viewed as molecular basis of memorization and they include enhancing and weakening of connections between neurons-synapses (Citri *et al.,* 2008).

There are three types of synaptic plasticity: developmental, short-term and long-term plasticity but only second and third concerns to learning. Developmental

synaptic plasticity is essential for brain development. Short-term synaptic plasticity relies on accumulation of calcium ions in pre-synapse and neurotransmitter release, leading to short-term memory. Long-term plasticity relates to long-term memory andis described further in detail (Citri *et al.,* 2008).

Long-Term Potentiation (LTP) leads to temporary enhancement of excitatory postsynaptic potential amplitudes. It is the type of neural plasticity which provides long lasting strengths to synapses. These changes include increased number and size of dendritic spines, higher number of receptors on post-synapse and increased number of ribosomes. In experimental protocols, LTP appears after high-frequency (tetanic) stimuli of pre-synapse or pairing stimulation. Pairing stimulation is a stimulation of pre-synapse with simultaneous depolarization of post-synapse (Citri *et al.,* 2008, Blair *et al.,* 2001). Naturally, LTP appears as an effect of theta rhythm which isan oscillatory pattern of brain activity with frequency around 6-10Hz. This rhythm appears during exploration and exposure on novelity (Citri *et al.,* 2008, Martin *et al.,* 2000, Winson *et al.,* 1974).

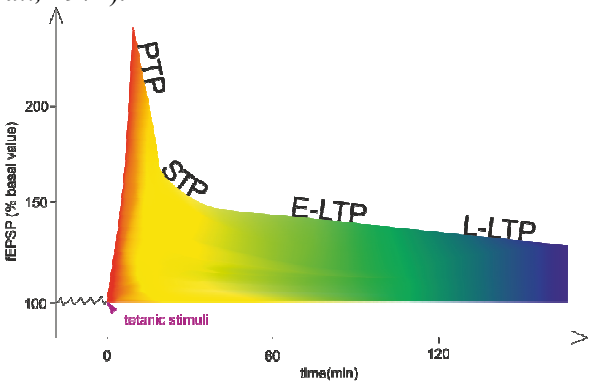

FIG.2. Scheme of post-synaptic Long-Term Potentiation. Horizontal axis illustrates time in minutes and vertical axis illustrates percentage of basal value of filed Excitatory Postsynaptic Potentials. Tetanic Stimuli provides to Post-Tetanic Potentiation (PTP) which depends on Ca^{2+} entry (red). After that appears Short-Term Potentiation (STP, yellow) which also depends on increased level of Ca^{2+}. Next phase is Early-LTP where some of kinases are activated. Last one, Late-LTP is based on protein synthesis and provides to long-lasting changes on synapse.

LTP is not a homogenous process and it can be divided into four phases and each phase is essential to create long-lasting synaptic changes and depends on different molecular basis (Sweatt *et al.,* 1999).

Post-tetanic potentiation (PTP) – It is the first phase of LTP and depends on Ca^{2+} entry into cytoplasm of post-synapse mediated by N-methyl-D-aspartate receptor (NMDAR). NMDAR open only in specific conditions: with co-activation of two ligands: glutamate and glycine (or D-serine). NMDAR is also blocked by magnesium ion which can be released by membrane. So opening NMDAR require co-activation of two pre-synapses (Nowak *et al.* 1984, Tsien *et al*., 2000, Malenka *et al.,* 1993).In some parts of brain (for examples CA1, medial nuclei of the amygdala) Ca^{2+} can flow also by other channels like Voltage-Dependent Calcium Channels type L (VDCC) which can also mediate LTP: with or without NMDAR (Chapman *et al.,* 1992).

Short-Term Potentiation (STP)-during this phase increased calcium level in cytoplasm is sustained by metabotropic glutamate receptors type 1 (mGluR1) (Erickson *et al.,* 2010). Binding glutamate to mGluR leads to activation of proteinG$_q$.G$_q$affects phospholipase C (PLC) which provides to formation of Diglyceride (DAG) and inositol-1,4,5-trisphosphate (IP3). In turn, IP3 activate IP3 receptors on smooth endoplasmic reticulum which is a calcium store in a cell (Alberts *et al.* 2013).

Nitrous oxide (NO) laso plays a crucial role in STP (Bernabeu *et al.,* 1995). NO acts retrogradely (on pre-synapse) and causes increased release of glutamate which expedites activation of glutamate receptors and thus increased Ca^{2+} entry (Alberts *et al.* 2013, Böhme *et al.,* 1991).

Early-LTP (E-LTP)–Increased calcium level in cytoplasm causes a cascade of changes in cellleading to an LTP- phase dependent upon kinases. Higher level of Ca^{2+} causes activation of protein kinase A (PKA) and calcium dependent kinase II (CaMKII).CaMKII phosphorylates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) which can be activated by glutamate, thus being permeable for Ca^{2+} (Lisman *et al.,* 2002, Derkach *et al.* 1999). CaMKII controls also RasGAP and provides increased activity of ras protein. In that way intracellular vessels with AMPARs heads to cell membrane which increase neuron excitability (Böhme *et al.,* 1991). Insertion of AMPAR to cell membrane is also regulated by Phosphoinositide 3-kinase (PI3K) which acts through protein kinase B (PKB, also known as AKT) on t-SNARE proteins. (Lisman *et al.,* 2002, Citri *et al.,* 2008).

Another important consequences of E-LTP are cytoskeletal changes which are caused by increased calcium level. Integrinsand cadherins are activated bytyrosine kinases, protein Src, p190 RhoGAP and finally Rho GTPase which suppress actin depolimerization factor-cofilin. Actin can polymerize and create actin skeleton which can build new dendritic spines (Lamprecht *et al.* 2004). However, Rho GTPase phosphorylates also collapsin response mediator protein (CRMP2) which is responsible for microtubules' polymerization. Phosporylated CRMP2 loses that properties and with its inactivation of microtubule skeleton is suppressed (Arimura *et al.,* 2005).

In E-LTP DAG has a role, by activating PKC and protein kinase G. Common place for all these kinases in LTP's pathway is mitogen-activated protein kinase (ERK, also known as MAPK). In one way, ERK phosphorylates potassium channels type A which increases potassium currents and excitability of neuron. In other, nearCaMKII, PKA, PKC and PKG, it is also an nuclear activator of cAMP response element-binding protein (CREB) (Silva *et al.,* 1998). CREB is an element of next phase of LTP- Late LTP (L-LTP).

Late-LTP- this phase relies on protein synthesis which contributes to long-lasting changes in synapses. Phosphorylated by kinases CREB creates a complex with

protein binding CREB (CBP) and in that complex it binds to specific region on DNA-CRE (Silva *et al.,* 1998). CREB is an activator of immediate early genes (IEGs) like *Arc, c-fos, Zif268* (Rosen *et al.,* 1998). Activation of *c-fos* leads to expression of matrix metallopeptidase 9 (MMP-9) which is responsible for maturation of dendritic spines. MMP-9 posible is released to an extracellular matrix where it can process laminins. Once laminins are processed it acts asa substrate for b1 integrins which there by polymerises actin and lengthens dendritic spines. MMP-9 also influences VDCCs and NMDARs, however the mechanism of its regulation is not clear. Intracellular substrate for MMP-9 is CRMP2, which is activated by cleaving. In that way microtubule skeleton mounts up (Stawarski *et al.,* 2014, Bajor *et al*. 2012).

Shortly after release of MMP-9 it is inactivated by tissue inhibitor of metalloproteinases 1 (TIMP1) and synapse gets mushroom-like shape (mature form of spine) (Stawarski *et al.,* 2014).

Postsynaptic Long-Term Depression

The second process providing long-lasting changes inn synaptic transmission is long-term depression (LTD). LTD leads to weakening of synaptic efficency. This state can be experimentally induced by low-frequency stimuli or chemically (by activation of mGluR) (Kemp *et al.,* 2007).

Induction of LTD. An enigmatic property of synaptic plasticity is that LTD just like LTP can be induced by activation of NMDAR or mGluR. What's more is this opposite state also depends on calcium ions entry to a cell (Kemp *et al.,* 2007).One hypothesis claims that the difference between activation of these processes is in the level of Ca^{2+}which enters to cytoplasm. In this hypothesis lower level of influent Ca^{2+} provides to LTD while higher provides to LTP. This hypothesis is consistent with different properties of some calcium detectors in LTP and LTD. For example activation of calmodulin (CaM) in LTD requires lower level of Ca^{2+}than activation of CaMKII in LTP (Lisman *et al.,* 1989).

Induction of LTD is based on NMDARs (especially containing subunit NR2B) or by mGluR (Kemp *et al.,* 2007, Yashiro *et al.,* 2008).These two ways of induction leads to different pathways so they will be described separately.

NMDAR-dependent LTD. In that type of LTD, Ca^{2+} is binded by CaM, which activates calcineurin and so on protein phosphatase 1 (PP1). PP1 suppress via dephosphorylation AMPARs and CaMKII (and thus LTP pathway). On the other hand, PP1 activates glycogen synthase kinase 3 beta (GSK3β) by its dephosphorylation (Collingridge *et al.,* 2010).

GSK3β through phosphorylation of kinesin light chain 2 suppress that motor protein and microtubul transport at once (vessels with AMPAR are not able to internalize with membrane). GSK3β phosphorylates also β-catenin which provides to its degradation. β-catenin creates adherent junctions between pre- and post-

synapsesothat degradation is therefore a possible cause of decreasing number of synapses after LTD (Bradley *et al.,* 2012, Kaidanovich-Beilin *et al.,* 2011).

Another effect of GSK3β is depolimerisation of microtubules. Increased cytoplasmic calcium level activates also protein interacting with PKC 1 (PICK1) which affects actin skeleton. Activated PICK1 binds to F-actin and Actin-Related Proteins 2/3-Arp2/3 which leads to actin (Collingridge *et al*., 2010).

mGluR-dependent LTD. Binding ligand to mGluR activates PLC and IP3 and DAG are created. IP3 provides to release of Ca^{2+} from smooth endoplasmic reticulum and this is direct source of increased cytoplasmic calcium level in that type of LTD (Collingridge *et al.,* 2010, Alberts *et al*. 2011).

DAG activates PICK1 (through PKC) which phosphorylates subunit of AMPAR. That subunit splits off from AMPAR-binding protein and glutamate receptor interacting protein (ABP/GRIP). It provides to internalization of AMPAR and lesser excitability of neuron (Collingridge*et al.,* 2010).

Some parts of these two types pathways are probably common. However, there is a need of determination of theirs cascades, especially on their nuclear level. It is only known that eukaryotic elongation factor 2 (EEF2) can be nuclear activator. Some researchers claim that its effect is a translation of Arc, Protein tyrosine phosphatases (PTPs) and p38 MAPK (Collingridge *et al.,* 2010).

Functions of LTP and LTD

LTP was a state observed during some types of learning and as described above- it was also observed as a consequence of theta rhythm in hippocampus. With its enhancing effect on synapsis it was a good candidate of molecular equivalent of learning (Rogan *et al.* 1997). LTD by contrast, as an opposite state matches perfectly as molecular basis of forgetting (Tsumoto *et al.,* 1993).

However, with further reports, it was clear that way of thinking do not describe properly memorization. Firstly, theta rhythm in some parts of brain (for example in the amygdala) causes LTD, not LTP (Heinbockel *et al*. 2000). Secondly, it seems that some types of fear conditioning is based rather on weakening than strengthen of synapses (Paré *et al.,* 2000). Finally, it was shown that blocking LTD (with LTP preserved) impairs contextual and spatial learning with no changes on non-contextual learning (Etkin *et al.,* 2006). However selective blocking of LTP (by blocking NMDAR subunit- NR2A) also impaired spatial learning (Kemp *et al.,* 2004).

On the other hand, it seems that in some types of associative learning LTP or LTD can be treated as an equality of memorization (with an opposite process as a forgetting). Associative learning is explained by theory of associative learning (also called Hebbian plasticity). Initially, Hebbian theory said that during repeatedly stimuli of two neurons, new synapses between these neurons are created. Later activation of one neuron would possess to activation alsopaired neuron (Citri *et al*., 2008). Now,

this theory is linked with Konorski's theory which says that learning modify pre-existing connections between these neurons. (Konorski, 1948).

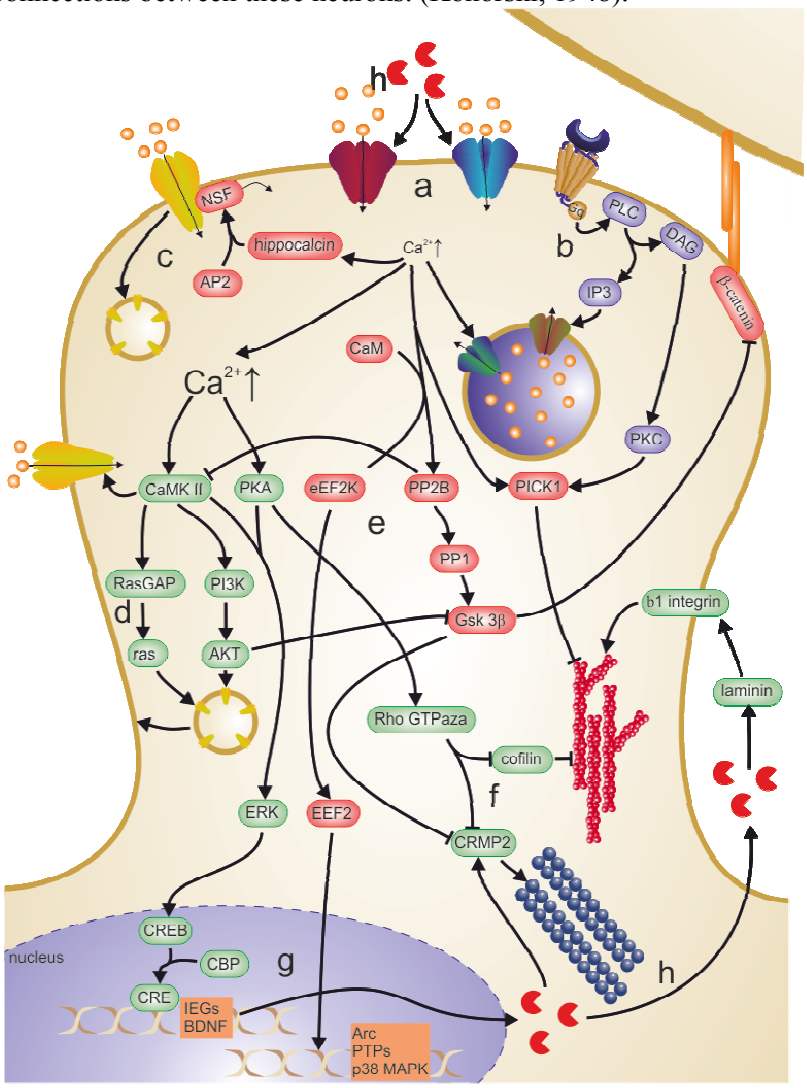

FIG.3: Pathway of postsynaptic LTP and LTD. Green frames concerns to LTP, red to LTD and blue are common for them. (a) Opening NMDARs and/or VDCCs provides to calcium ions entry. (b) Increased cellular level of calcium can be achieved also via mGluRs. (c) Minor increase of Ca^{2+} level activates hippocalcin which leads to AMPARs internalization. (d) Higher level of intracellular Ca^{2+} activates LTP cascade. Vessels with AMAPR are transferred to cell membrane. (e) During LTD microtubules and actin are depolymerized. Junctions between pre- and post-synapse break off. (f) Long-lasting changes on synapses require changes of microtubule and actin skeletons. (g) To long lasting changes,both LTP and LTD require synthesis of new proteins. (h) Activation of *c-fos*provides to activation of MMP-9 which affects cytoplasmic skeleton (synapse maturation) and permeability of NMDARs and VDCCs.

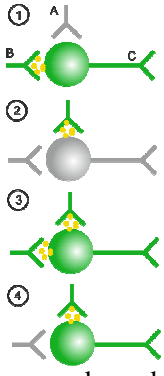

FIG.4. Scheme of associative plasticity. A- cell of conditioned pathway, B-cell of unconditioned pathway, C-integrative cell. In first situation activity of B (in Pavlovian experiment it will be cell carrying a information about food) excites C. In second situation,A (in Pavlovian experiment it will be cell carrying an information about light) can not excite C. Pairing A and B in third situation excites C but also strengthen connection between A and C. In fourth, A is enough to excite C.

Upon new knowledge about molecular basis of learning it seems that there is a big need of wariness during interpretation of data about synaptic plasticity. Treating LTP as equality of memorization and LTD as equality of forgetting is too big simplifying. Probably some research about impact of various substances on LTP/LTD and learning should be reconsidered (Chen *et al.* 2014). It should be remembered that affecting on one type of synaptic plasticity often changes also an opposite. One solution to better understanding of LTP and LTD is using diversity of behavioral tests which can verify different types of memory.

Better understanding of LTD and LTP can also shed light onto some of unsolved questions. In research with mice lacking genes for MMP-9 have got impaired reward learning with intact aversive learning (Knapska *et al.,* 2013). Upon a fact there is no activity of MMP-9 during LTD, it can be assumed that studied aversive learning (fear conditioning) was based rather on LTD than LTP.

It is still not clear how engrams are created and stored. It looks that proper learning requires balance between LTP and LTD. Especially, coding parts of declarative memory stays as guesses. One hypothesis claims, that during learning (with accompany of LTP) excess of active synapses is created. In that hypothesis, following LTD is necessary to stabilize neural network (Caroni *et al.,* 2012). Some scientists claim that this rearrangement (at least in the hippocampus) is a process where engrams are encoded on a matrix, created during LTP (Kemp *et al.,* 2007).

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