NEUROPLASTICITY

"EVERY MAN CAN, IF HE DESIRES, BECOME THE SCULPTOR OF HIS OWN BRAIN"
- Santiago Ramón y Cajal

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Santiago Ramón y Cajal at age 85

INTRODUCTION & OBJECTIVES

Neuroplasticity or **brain plasticity** is the ability of the brain to rearrange the neurological pathways that result in changes in function and behavior. This changes occur in a molecular and cellular level and it also involves gene expression. The aim of this work is to understand what is brain plasticity, how it works at a cellular and molecular level as well as to understand the structural changes that occur at the synapses during this process and how to apply this knowledge in the field of biomedicine.

METHODS & MATERIALS

My interest in brain plasticity came from a book called 'The brain that changes itself' by Nomran Doige, M.D. This thesis is based on information that provides this book and additional information from other resources such as scientific articles, interactive videos such as TED talks by most famous neuroscientists, and books that explain how the plasticity works in the brain and what are the molecules and mechanisms involved in it. The same type of data that relates plasticity to pathologies and therapies for neurological diseases was used.

MECHANISMS INVOLVED IN NEUROPLASTICITY

Cellular Mechanisms of plasticity

One of the mechanisms that involve plasticity it's the rearrangement and formation of new synapses. At the molecular level it has been discovered that there are two forms of long-term plasticity: long-term potentiation (LTP) and long term depression (LTD). LTD depends on NMDA and AMPA receptors

- **Long term potentiation (LTP)** is a persistent increase in synaptic strength following high-frequency stimulation of chemical synapse.
- **Long term depression (LTD)** is induced by delivery of low frequency stimulation. LTD is dependent on activation of NMDA and internalization of AMPA.

Molecules involved in neuronal plasticity:

NAME OF MOLECULE	TYPE OF MOLECULE	ACTIVATED BY	ROLE IN PLASTICITY
AMPA receptor	Ion channel glutamate receptor	Binding to glutamate	Once glutamate binds, allows Na+ and K+ ions to go inside of the cell and this cause activation of NMDA. LTP is produced when phosphorylation of subunit GluR1 in residue Ser831 occurs. To maintain LTP AMPAr maintains in the membrain is needed.
NMDA receptor	Ion channel glutamate receptor	Binding to glutamate	When the postsynaptic membrane depolarizes due to increase in ions that enter trough AMPAr glutamate binds. Calcium enters the cell and activates cascades that involve LTP and LTD induction.
Glutamate	Neurotransmitter	Released by changes in membrane potential	Neurotransmitter released by the presynaptic membrane that binds to glutamate receptors present on the postsynaptic membrane.
CaMKII	Serine/threonine kinase	Calcium	CaMKII binds to NMDA in the postsynaptic neuron. This allows this kinase to be near the calcium influx, stabilize its catalytic activity and phosphorylate AMPA. This phosphorylation induces LTP. It has an important role in learning and memorizing, thus is an important molecules in plasticity.
PP1	Phosphatase	Calcium	PP1 plays an important role in LTD. It enhances GSK-3 dephosphorylated form at the postsynaptic neuron, allowing LTD induction.
Hippocalcin	Calcium binding protein	Calcium	Activates complex NSI-AP2 at the postsynaptic neuron. This cause AMPAr internalization and for that LTD expression.
PI3K	Protein Kinase	Calcium	Activates Akt.
GSK-3	Serine/threonine kinase		Inhibits AMPAr internalization and for that helps maintenance of LTP.
Caspase-3	Caspase protein		Activates Akt.
Akt	Protein Kinase B also known as PKB	PI3K	Activates phosphorylated form of GSK3.

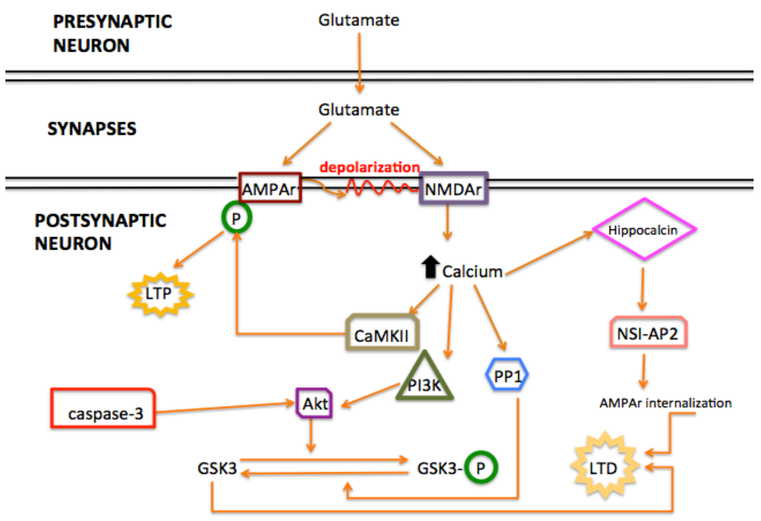


Figure 1: Scheme of the cellular mechanism underlying neuronal plasticity

Activity dependent gene expression

New gene transcription and expression is required to have persistent LTP and to maintain for more than a few hours, the structural changes that occur in the synapse. The gene expression allows the synthesis of new proteins that will take part in the synapses.

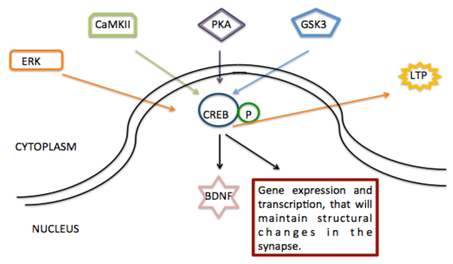


Figure 2: Activation of CREB by different types of molecules.

- CREB most important transcription factor to maintain LTP and LTD.
- CREB can be activated by different cascades, most important are CaMKII, GSK3 and PKA.
- Blockage of PKA pathway impairs LTP expression.
- At late- phase LTP there is an increase in phosphorilation of CREB
- The ERK pathway helps maintain phosphorylation of CREB and therefore it helps maintain LTP.

After learning and memorizing our post synaptic sites undergo a series of structural and morphological modifications that stabilize after hours or days. Most of these changes are due to gene expression and protein synthesis.

- The increase in intracellular calcium produces a rearrangement of the cytoskeleton at the synapse. The cytoskeleton is formed by actin microfilaments.
- Changes occur in the dendritic spines. This spines contain the post synaptic density (PSD).
- PSD includes receptors, channels and signalizing molecules.
- Induction of LTP cause 3 types of changes in the spines they are shown in Figure 3 and they are the following:
  1. Change in size of the button -> increase in number of neurotransmitters, presynaptic vesicles and postsynaptic ribosomes
  2. Formation of new spines -> enhances transmission
  3. Increase of the size of the spines
- Ability to change depends on the actin microfilament polymerization.
- Blockage of NMDA -> NO LTP -> NO POLYMERIZATION
- Rho ATPase regulates the skeleton morphology by regulating the cytoskeleton
- Also adhesion molecules are involved in this process and this are integrin, cadherin, neurexin and immunoglobulin superfamily
- Cadherin also associates with Rho GTPase to regulate cytoskeletal rearrangements.

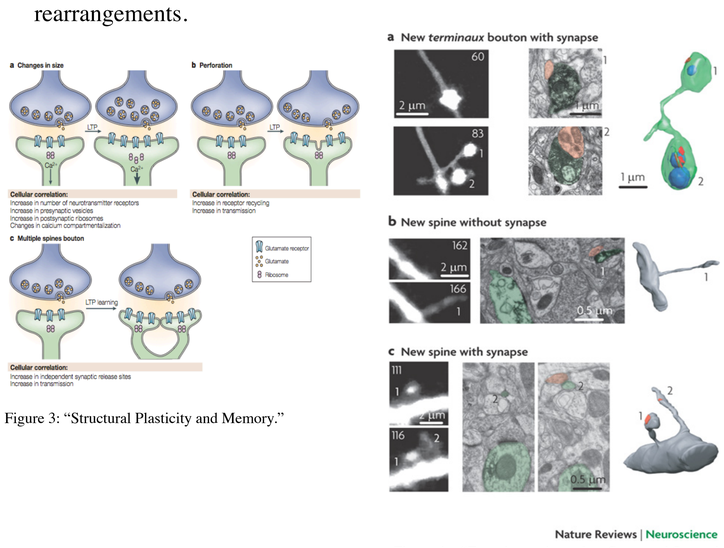


Figure 3: "Structural Plasticity and Memory."

Figure 4: , "Experience-dependent Structural Synaptic Plasticity in the Mammalian Brain."

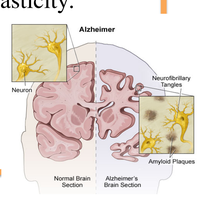
PATHOLOGIES AND THERAPY

Our brain is no longer hardwierd. By **exercising** our brain we could change and strengthen our neurological pathways and connections. We have to use plasticity to help people that suffer with learning disabilities, brain injuries, strokes, psychological problems, pain, and obsessions...

HOW?

- Finding therapies that allow the healthy parts of the brain to take over functions of those areas that are damaged.
- Forming new brain maps and new connections between the healthy neurons.
- Reopening the critical period, which is the period when our brain has maximum plasticity.
- Turning on the nucleus basalis.
- Repetition of tasks in those patiens who suffer from brain injuries.
- Creating therapies that induce LTP in rats that are models of Alzheimer Disease.

We have to work hard and never give up on this research!!



CONCLUSIONS

1. The brain is a complex organ, which in many ways remains a mystery to us.
2. To master brain plasticity we have to understand:
   - Mechanism of LTP and LTD expression.
   - Cellular and signalizing pathways that take place in the synapse.
3. Key Molecules:
   - CaMKII
   - GSK3
   - PKA

   } Alteration of this molecules → impair on learning and memorizing → we won't be available to sculpture our brain.

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