Chapter 8

# Redox Homeostasis in Neural Plasticity and the Aged Brain

Pablo Muñoz, Francisca García, Carolina Estay, Alejandra Arias, Cecilia Hidalgo and Álvaro O. Ardiles

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63931

**Abstract**

Currently, humans can easily live for 60 years and more. This increase in life expectancy produces myriad changes in our bodies that diminish the individual's physical and mental capacities and affect as well the functional capacity of individuals to interact appropriately with their social and physical environments. The oxidative theory of aging predicts an accumulation of oxidative damage to proteins, lipids, and DNA with age; as a consequence, the aged brain gradually suffers loss in neuronal functions, increasing the risk of developing neurodegenerative diseases and cognitive impairment. To date, there are no effective treatments to prevent age-related cognitive decline, making it urgent to identify the neural mechanisms that are altered during aging. In this chapter, we discuss the mechanisms that underlie synaptic plasticity, emphasizing the relationship between redox balance and neuronal function, and we also address current evidence supporting oxidative stress as an important contributing factor in brain aging.

**Keywords:** synaptic plasticity, aging, neuronal function, oxidative stress, cognitive decline

## 1. Introduction

Currently, humans can easily live for 60 years and more. This increase in life expectancy produces myriad changes in our bodies that diminish the individual's physical and mental capacities and that affect as well the functional capacity of the individual to interact appropriately with the environment. To date, there are no effective treatments to deter the age-related cognitive decline.

Thus, in order to identify potential therapeutic targets and thus improve the quality of life of aging individuals it becomes urgent to decipher the neural mechanisms that are altered during aging. This knowledge will allow the design of molecules for the prevention, delay or even the reversal of age-related cognitive malfunction.

During aging, the brain undergoes a progressive accumulation of oxidative damage to macromolecules, such as synaptic proteins, lipids, and DNA, which gradually alters neuronal functions and increases the risk of developing neurodegenerative diseases and cognitive impairments.

As you would expect, various nutritional interventions that somehow prevent or counteract this oxidative accumulation, they have proved effective in mitigating the effects of brain aging. Although there is no consensus, the evidence suggests that the consumption of dietary antioxidants may have a beneficial effect on the mental health of aging individuals by a mechanism that involves improvement of synaptic plasticity (SP) [1], as well as an increase in the flow of blood and neurogenesis [2]. Caloric restriction, a significant decrease in caloric intake, is another nutritional intervention in animal models with positive impact in synaptic plasticity, which produces attenuation in the effects related to aging in the CA3 region of the hippocampus [3, 4].

In particular, aging entails synaptic failure, so to achieve a better understanding of the changes associated with the aging process and how to prevent, it is necessary to understand how it affects the mechanisms underlying synaptic plasticity.

This chapter discusses the following topics:

**a.** Cellular mechanisms of synaptic plasticity.

**b.** Redox regulation mechanisms acting in synaptic plasticity.

**c.** Disturbances of neuronal redox homeostasis and accumulation of oxidative damage during aging.

## 2. Cellular mechanisms of synaptic plasticity

Synaptic plasticity, defined as functional and structural changes occurring in the synapse in response to specific neuronal activity, is critical for the processing of information by the brain. It is widely accepted that changes in synaptic connections, which represent the cellular basis of memories, are encoded and stored in the central nervous system. At the cellular level, these changes occur when a postsynaptic neuron responds to a given presynaptic stimulation caused by either depolarization or neurotransmitter release. This postsynaptic response initiates a series of metabolic changes that promote, in turn, the stimulation of gene expression necessary to enable and consolidate long-lasting structural and functional changes. In its most general form, the hypothesis linking SP and memory states that neuronal activity-dependent plasticity is induced in certain synapses during memory formation. This fact is necessary and sufficient to store information, outlining the type of memory involved in the area of the brain in which plasticity is observed [5–7].

http://dx.doi.org/10.5772/63931

At the electrophysiological level, SP entails an increase or a decrease in synaptic efficiency; these changes are known as long-term potentiation (LTP) (**Figure 1**) or long-term depression (LTD), respectively [8]. If changes occur on the same synapse that was stimulated, they give rise to homosynaptic plasticity. Alternatively, if changes occur in synapses other than those stimulated, they originate heterosynaptic plasticity [9, 10]. The cellular and molecular mechanisms of LTP and LTD have been extensively studied in the hippocampus [11], an area involved in the formation of spatial memory in rodents and humans. In the hippocampus, many forms of plasticity, including LTP and LTD, require an increase in calcium concentration in the postsynaptic neuron [7, 12, 13].

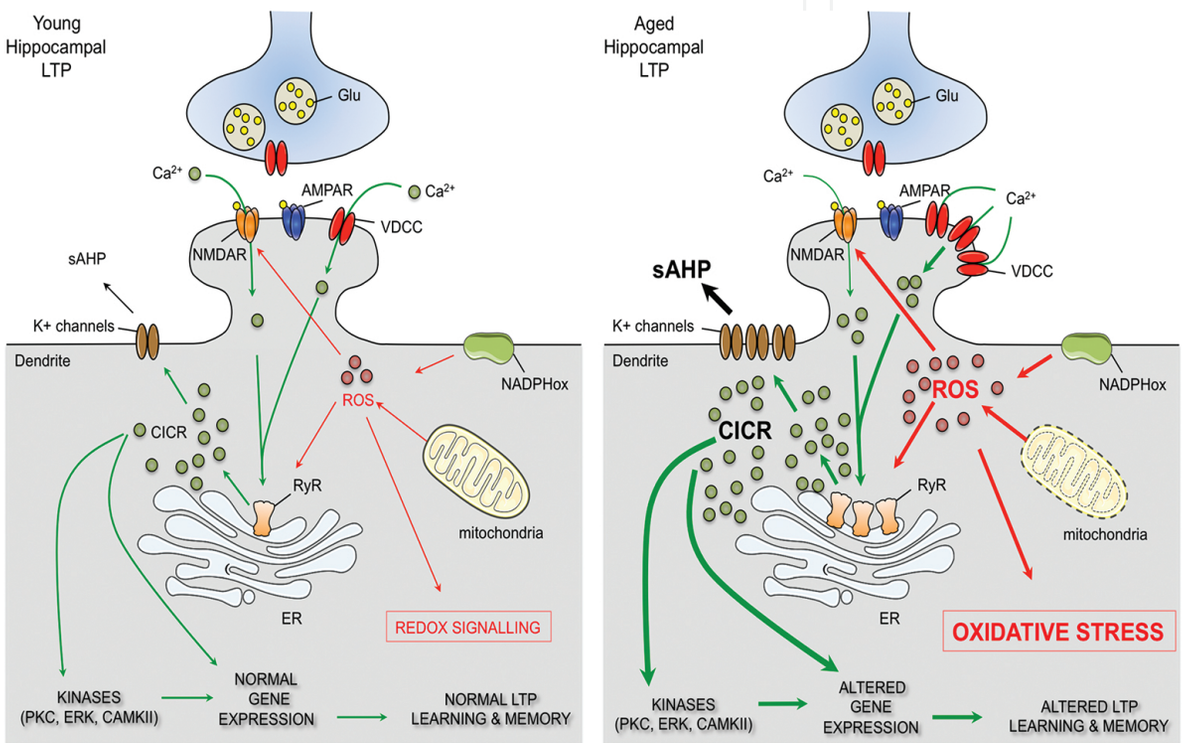


**Figure 1.** Cartoon depicting the signaling pathways involved in synaptic plasticity. In response to glutamate, NMDA (N-methyl-D-aspartate) receptors (NMDARs) and L-type voltage-dependent calcium channels (VDCCs) open allowing the influx of calcium into the cell. The increase in cytosolic calcium concentration activates the release of calcium from the endoplasmic reticulum (ER) by ryanodine receptors (RyRs) through a calcium-induced calcium-released mechanism (CICR) amplifying calcium signaling. In young synapses, this calcium elevation leads to the activation of calcium-dependent kinases, which are relevant to synaptic plasticity and learning and memory. NMDAR activation also induces the generation of ROS by the activation of NADPH oxidase. Mitochondrial-generated ROS can also contribute to the increase of calcium concentration through the modulation of the activity of NMDARs and RyRs. In aged synapses, the generation of ROS by mitochondria is exacerbated leading to oxidative stress. Ion imbalance, lipoperoxidation, DNA damage, and metabolic impairment are signatures of aged conditions. Increased density of VDCC and calcium-dependent potassium channels produce an increase of the slow component after hyperpolarization (sAHP), contributing to the aging process.

In the hippocampal CA1 area, activity-dependent postsynaptic calcium increments are initiated by calcium influx from the extracellular space through glutamate receptors of the N-methyl-D-aspartate (NMDA) type or through voltage-dependent calcium channels (VDCCs) (**Figure 1**). The resulting calcium signals are amplified and propagated through the calcium-

induced calcium release (CICR) mechanism, which engages calcium release from intracellular stores [14]. Much of the experimental work concerning the possible role of LTP in learning has been focused on NMDA receptor (NMDAR)-dependent LTP [15–19]. These studies have shown that pharmacological NMDAR blockage impairs both learning and SP [16, 18–20]. Similarly, spatial memory is impaired in mice with a mutation in the NMDAR R1 subunit; this impairment correlates with alterations in LTP or LTD [21]. Hippocampal NMDAR-dependent SP includes classical associative long-term plasticity between the perforant/dentate gyrus pathway and between neurons in the CA3 and CA1 circuits; the coupling between the excitatory postsynaptic potentials (EPSPs) is associated with action potentials [22]. In addition, post-tetanic potentiation (PTP) and paired pulses facilitation (PPF) are two forms of short-term plasticity, which critically require NMDAR activation [23–25]. A number of NMDAR-independent SP also occur in the hippocampus, including LTP between the mossy fibers of the dentate gyrus and CA3 neurons; this plasticity is induced by the brief application of certain growth factors or neurotransmitters [26, 27].

At glutamatergic synapses, glutamate released from the presynaptic vesicles diffuses across the synaptic cleft and then binds to ionotropic receptors for $\alpha$-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and to NMDAR present in the postsynaptic membrane. The activation of AMPA receptors (AMPARs) allows sodium influx and potassium efflux through these channels, causing excitatory postsynaptic currents and transient postsynaptic depolarization, which can be recorded as EPSP. This depolarization allows the removal of NMDAR blockage by magnesium ions ($Mg^{2+}$), which occurs under resting conditions and prevents ion conduction through the channel. However, the strong depolarization is typically achieved during a train of high-frequency presynaptic activity or direct current injection to the postsynaptic neuron, release $Mg^{2+}$ from the channel pore, leading to NMDAR opening and allowing calcium/sodium influx into the postsynaptic terminal [28].

Calcium ion ($Ca^{2+}$) is a versatile cellular messenger engaged in numerous functions, including muscle contraction, apoptosis, cell growth, cell proliferation, synaptic plasticity, and gene expression regulation [29]. The extracellular $Ca^{2+}$ concentration ranges from 1.5 to 2 mM, whereas the intracellular resting concentration is four orders of magnitude lower and ranges from 70 to 100 nM [30–32]. Increments in neuronal intracellular calcium concentration are of great physiological importance because they play an important role in neuronal functions such as neurotransmitter release, excitability, neuronal plasticity, and gene expression, all functions that are associated with SP and memory formation [30, 31, 33, 34]. In particular, postsynaptic calcium influx triggers amplification and signal propagation by CICR; this process involves the activation of intracellular calcium channels present in endoplasmic reticulum (ER) [14, 30, 34, 35], a continuous membranous network distributed throughout the neuronal cell, including dendrites and dendritic spines, the soma, and the surrounding the nucleus and extending into the axon to reach the presynaptic terminals, where it is closely associated with mitochondria [36] (**Figure 1**).

Two different types of intracellular calcium channels are involved in calcium release from the ER: the inositol 1, 4, 5-trisphosphate (IP3) receptor (IP3R) and the ryanodine receptor (RyR) channels [14, 30, 34, 35]. In areas such as the hippocampus, calcium release is mediated

primarily through RyR [37] (**Figure 1**), providing the largest share of the increase of calcium in the postsynaptic spines. The RyR channel has been cloned, purified, and sequenced from several species. Three isoforms of this receptor have been identified: RyR1, RyR2, and RyR3, each one encoded by a different gene. All three RyR isoforms have about 5000 amino acid residues and present 65% of identity among them [38, 39]. RyR1 is the isoform primarily expressed in skeletal muscle, RyR2 in cardiac muscle, and RyR3 in diaphragm muscle [34, 40, 41]. All isoforms are expressed in the brain, RyR2 being the most abundant isoform [41–43]. At the anatomical level, RyR channels have been found in the frontal cortex, olfactory bulb, thalamus, amygdala, cingulate cortex, piriform cortex, entorhinal cortex, occipital cortex, and hippocampus [40–42, 44].

The ryanodine receptor is a homotetramer with a molecular mass of >2 MDa in which each subunit has a weight of ∽560 kDa [38, 39]. It has a large N-terminal segment located in the cytoplasm that represents about 90% of the protein, while its C-terminal is small and also facing the cytoplasm. The presence of a large N-terminal site allows its scaffold function for various proteins that play central roles in signal transduction pathways mediated by calcium [45]. The RyR channel can be activated by calcium, caffeine, 4-chloro-m-cresol (4-CMC), and ryanodine, the alkaloid from which its name comes. However, ryanodine has a dual effect on the receptor because at low concentrations (<1 μM) it activates the channel, whereas at high concentrations (>10 μM) it abolishes channel activity [37, 46]. RyR channels are also susceptible to inhibition by dantrolene and are modulated by adenosine triphosphate (ATP), H+, $Mg^{2+}$, kinases, phosphatases, and reactive oxygen species (ROS) [38].

Different authors have shown that RyR-mediated $Ca^{2+}$ signals have a role in SP, learning, and memory. In primary hippocampal cultures, RyR agonists such as ryanodine and caffeine generate calcium signals that trigger neuritic growth [47] as well as dendritic remodelling [43]. At the electrophysiological level, RyR inhibition by inhibitory concentrations of ryanodine suppresses sustained LTP, while ryanodine concentrations that activate RyR promote hippocampal LTP induction [48]. Moreover, RyR2/RyR3 expression in young rats increases after a hippocampal-dependent behavioral task [43, 44].

Using a genetic approach, it has been demonstrated that the absence of the RyR2 or the RyR3 isoforms, but not of RyR1, impairs spatial memory, while ryanodine concentrations that activate RyR channels promote memory consolidation in rats [39], mice [49], and chickens [50]. By contrast, the RyR inhibitor dantrolene alters spatial memory [35].

## 3. Reactive oxygen species in synaptic plasticity

As mentioned in the previous section, NMDAR activation is required for various forms of hippocampal plasticity, which produce a number of second messengers, including cAMP, nitric oxide, arachidonic acid, and, certainly, calcium. Recently, ROS have been added to the list of molecules generated upon activation of NMDAR [51, 52].

The role of ROS as synaptic transmission modulators is complex and depends on the concentration and duration of the oxidant stimulus [53, 54]. However, after LTP induction, neuro-

nal ROS generation has been detected [54, 55]. This observation not only suggests that ROS may be necessary for LTP induction but also suggests that ROS generation is important for normal neuronal activity, as discussed subsequently.

Pharmacological activation of NMDAR induces the production of superoxide ($O_2^{\cdot-}$) [51], which raises the question of whether ROS generation meets some physiological function. Ascribing to $O_2^{\cdot-}$ only a neurotoxic effect is not correct, because inhibition of $O_2^{\cdot-}$ production results in significant reduction of LTP induction [54, 55]. The NADPH oxidase complex is a recently characterized superoxide-generating source during NMDAR activation in neurons [52, 56]. This oxidase has been extensively characterized in immune cells [57, 58], but compelling evidence also suggests that superoxide anion generation mediated by this enzyme plays an important role in LTP induction. Incubation of brain slices with superoxide dismutase (SOD), an antioxidant enzyme that catalyzes the removal of superoxide, or with permeable and impermeable superoxide scavengers results in LTP attenuation [55, 59, 60]. Consistent with the above reports, hippocampal LTP is also affected in transgenic mice overexpressing Cu/Zn-SOD isoform [59, 61]. Thus, superoxide anion may be produced as a result of, or in conjunction with, other molecules necessary for LTP. Although superoxide has been implicated to SP-related kinases, such as protein kinase C (PKC) [62] and extracellular signal-regulated kinase (ERK) [63], its mechanism of action is not yet defined.

In addition to the modulating effect of superoxide on SP and memory, hydrogen peroxide ($H_2O_2$) also affects signaling pathways involved in SP [64]. For instance, $H_2O_2$ regulates the activity of several kinases, such as PKC and the mitogen-activated protein kinase (MAPK) family [65–67], as well as phosphatases such as calcineurin [66]. Accordingly, incubation of hippocampal slices with catalase, an enzyme that degrades $H_2O_2$ to water, exhibits altered hippocampal LTP, further supporting a role for $H_2O_2$ in SP [53, 68, 69].

Remarkably, another electrophysiological study reported conflicting results that are difficult to interpret [53], illustrating the complexity of redox signaling. Using hippocampal slices, it was found that a high concentration of $H_2O_2$ reduces synaptic responses, while exposure to an intermediate concentration has no apparent effect on the expression of pre-established LTP, but prevents induction of a new LTP. Surprisingly, a low concentration of $H_2O_2$ increased LTP expression compared to control (absence of peroxide). Another important effect of a low concentration of $H_2O_2$ is the suppression of LTD [53]. It seems that high concentrations of $H_2O_2$ can give rise to secondary oxidative reactions unrelated to a physiological response; by contrast, low concentrations of $H_2O_2$ can be part of the normal mechanism for LTP induction.

Within the context of ROS as cellular messengers, both Fenton and Haber-Weiss reactions are catalyzed by iron and involve superoxide anion and hydrogen peroxide. This feature implies that the mentioned reactions may have biological relevance [70]. While there are few studies that make a direct relation between iron-generated ROS and SP [71, 72], there are clinical data showing that iron deficiency during childhood has a strong impact on some cognitive functions related to SP and that this effect persists in the adult individual despite restoration of normal iron levels [73–75].

http://dx.doi.org/10.5772/63931

## 4. Redox imbalance in the aged brain

One of the most plausible theories of aging, which involves free radicals, was proposed by Harman in the mid-1950s [76]. This theory suggests that free radicals generated during aerobic metabolism produce cumulative damage in various cellular components, resulting in a loss of function characteristic in the physiology of organisms during aging. Subsequently, this hypothesis was refined including mitochondria as the main source of free radical production in physiological processes [77], as the inner membrane of mitochondria consumes nearly 90% of the oxygen generated by cellular respiration. According to this theory, ROS generated as by-products produce oxidative stress that damages the mitochondria itself, which results in dysfunctional mitochondria with the passing of years.

Particularly, the brain is sensitive to oxidative damage due to several factors. Among them, we can mention its mitochondrial high metabolic rate, the presence of high concentrations of polyunsaturated fatty acids, the presence of transition metals such as iron that are involved in the generation of the hydroxyl radical and the consequent lipid peroxidation, and, finally, a lower antioxidant capacity compared with other organs [78, 79].

This theory predicts that by controlling oxidative stress it is possible to delay the effects of aging. However, studies in *Drosophila melanogaster*, *Caenorhabditis elegans*, and mice, in which the expression of antioxidant genes was experimentally increased, did not achieve the expected impact on lifespan [80–82]. Furthermore, a recent study using post-mortem brains showed no significant differences in glutathione levels in aged individuals compared to younger ones, although a number of increments were found in some brain regions as the frontal and occipital cortex, caudate nucleus, and cerebellum [83]. The fact that this theory cannot fully explain the changes associated with aging shows how complex and multifactorial the aging process is.

Evidence supporting this theory in patients or in Parkinson's and Alzheimer's disease animal models suggests a decrease of glutathione and glutathione transferase activity with age in selected areas of the brain and ventricular cerebrospinal fluid [84]. In this regard, it has been described that ROS and oxidative damage may contribute to cerebral aging and also to a higher prevalence of neurodegenerative diseases. Thus, whereas diverse evidences correlate neuronal changes in redox status with progressive aging in the brain [85–90], others show that the cumulative effect of oxidative stress in neurodegenerative diseases may depend on the organism [91]. Multiple lines of evidence suggest that in the brain changes in the redox environment induce cognitive decline with age, by alterations in synaptic function or intracellular calcium regulation [92, 93]. Aging is associated with impairment in the ability to store, retain, and retrieve information, affecting declarative memory in humans, primates, dogs, and rodents [94–98].

Initially, the deficit in cognitive function associated with aging was partly attributed to a decrease in the number of neurons in the hippocampus [31, 36, 99], a critical region for spatial memory [100–102], or by diminished activity in the prefrontal cortex, the brain area involved in working memory, attention, and planning [95, 103]. However, subsequent studies reported that the loss of neurons does not contribute significantly to the cognitive decline

associated with aging; rather, a decrease in synaptic connectivity has been linked to cognitive impairment [99, 104]. On the other hand, numerous evidences suggest that cognitive impairment associated with aging may be due to changes in gene expression [40, 102, 105–109], alteration of calcium homeostasis [32, 93, 110, 111], or changes in the redox state of the cell [14, 34, 86]. All these changes will trigger alterations in the LTP and LTD, two models of SP considered the cellular mechanism of learning and memory [112].

Intracellular calcium deregulation affects a number of synaptic components and calcium-dependent processes [31, 113]. The activity of NMDAR depends on neuronal redox state, so that variations of oxidative stress strongly impact both synaptic responses and NMDAR-dependent plasticity [88, 90]. This property is of great interest since the spatial memory impairment occurred in middle-aged animals is also dependent on NMDAR function [114]. Interestingly, manipulating ROS levels by genetic overexpression of antioxidant enzymes has revealed a direct relationship between the cognitive impairment in aged animals and the regulation of NMDAR [89].

Another synaptic process affected by aging is the increase in the slow component of the $Ca^{2+}$ activated $K^{+}$- after hyperpolarization (sAHP) in neurons of the hippocampal CA1 region in aged rodents [115–117]. While it has been described that the sAHP can be modified by an increase in L-type voltage-dependent calcium channels [102, 105] or an increase in calcium-dependent potassium channel density [118], enhanced calcium release from intracellular compartments could also make a significant contribution [85, 111, 119]. In fact, among these factors, the latter becomes crucial because oxidative stress increases during aging and RyR channels are highly sensitive to cellular redox state, increasing their activity in response to oxidation [34, 120, 121].

Certainly, further research is needed in the search to understand and combat the deleterious effects of aging; knowledge gained from these studies should help the development of effective treatments for brain pathologies associated with aging.

## Acknowledgements

I like to thank Dr. Mario Párraga for his valuable comments and review of the manuscript.

## Author details

Pablo Muñoz[1,2*], Francisca García[1], Carolina Estay[1], Alejandra Arias[3], Cecilia Hidalgo[3,4] and Álvaro O. Ardiles[5]

*Address all correspondence to: pablo.munozca@uv.cl

1 Department of Pathology and Physiology, School of Medicine, Universidad de Valparaíso, Valparaíso, Chile

2 Interdisciplinary Center for Health Innovation, Universidad de Valparaíso, Valparaíso, Chile

3 Biomedical Neuroscience Institute, Faculty of Medicine, Universidad de Chile, Santiago, Chile

4 Institute of Biomedical Sciences and Center for Molecular Studies of the Cell, Faculty of Medicine, Universidad de Chile, Santiago, Chile

5 Interdisciplinary Center for Neuroscience, Universidad de Valparaíso, Valparaíso, Chile

## References

[1] Dias, G.P., et al., *The role of dietary polyphenols on adult hippocampal neurogenesis: molecular mechanisms and behavioural effects on depression and anxiety*. Oxid Med Cell Longev, 2012. 2012: p. 541971.

[2] Spencer, J.P., *The impact of fruit flavonoids on memory and cognition*. Br J Nutr, 2010. 104 Suppl 3: pp. S40–7.

[3] Adams, M.M., et al., *Caloric restriction and age affect synaptic proteins in hippocampal CA3 and spatial learning ability*. Exp Neurol, 2008. 211(1): pp. 141–9.

[4] Mladenovic Djordjevic, A., et al., *Long-term dietary restriction modulates the level of presynaptic proteins in the cortex and hippocampus of the aging rat*. Neurochem Int, 2010. 56(2): pp. 250–5.

[5] Kandel, E.R. and J.H. Schwartz, *Molecular biology of learning: modulation of transmitter release*. Science, 1982. 218(4571): pp. 433–43.

[6] Lynch, G. and M. Baudry, *The biochemistry of memory: a new and specific hypothesis*. Science, 1984. 224(4653): pp. 1057–63.

[7] Bailey, C.H., E.R. Kandel, and K.M. Harris, *Structural components of synaptic plasticity and memory consolidation*. Cold Spring Harb Perspect Biol, 2015. 7(7): p. a021758.

[8] Sweatt, J.D., *Neural plasticity & behavior – sixty years of conceptual advances*. J Neurochem, 2016.

[9] Nguyen, P.V., *Heterosynaptic strengthening of hippocampal LTP*. Trends Neurosci, 2001. 24(9): pp. 502–3.

[10] Kirkwood, A. and M.F. Bear, *Homosynaptic long-term depression in the visual cortex*. J Neurosci, 1994. 14(5 Pt 2): pp. 3404–12.

[11] Stanton, P.K., *LTD, LTP, and the sliding threshold for long-term synaptic plasticity*. Hippocampus, 1996. 6(1): pp. 35–42.

[12] Ni, Z., et al., *Heterosynaptic modulation of motor cortical plasticity in human*. J Neurosci, 2014. 34(21): pp. 7314–21, doi: 10.1111/jnc.13580.

[13] Connor, S.A. and Y.T. Wang, *A place at the table: LTD as a mediator of memory genesis*. Neuroscientist, 2015.

[14] Paula-Lima, A.C., T. Adasme, and C. Hidalgo, *Contribution of Ca2+ release channels to hippocampal synaptic plasticity and spatial memory: potential redox modulation*. Antioxid Redox Signal, 2014. 21(6): pp. 892–914.

[15] Baker, K.B. and J.J. Kim, *Effects of stress and hippocampal NMDA receptor antagonism on recognition memory in rats*. Learn Mem, 2002. 9(2): pp. 58–65.

[16] Gould, T.J. and M.C. Lewis, *Coantagonism of glutamate receptors and nicotinic acetylcholinergic receptors disrupts fear conditioning and latent inhibition of fear conditioning*. Learn Mem, 2005. 12(4): pp. 389–98.

[17] Jia, Z., et al., *Selective abolition of the NMDA component of long-term potentiation in mice lacking mGluR5*. Learn Mem, 1998. 5(4–5): pp. 331–43 doi:10.1177/1073858415588498.

[18] Torras-Garcia, M., et al., *Reconsolidation after remembering an odor-reward association requires NMDA receptors*. Learn Mem, 2005. 12(1): pp. 18–22.

[19] Fanselow, M.S., et al., *Differential effects of the N-methyl-D-aspartate antagonist DL-2-amino-5-phosphonovalerate on acquisition of fear of auditory and contextual cues*. Behav Neurosci, 1994. 108(2): pp. 235–40.

[20] Mao, Y., et al., *Early chronic blockade of NR2B subunits and transient activation of NMDA receptors modulate LTP in mouse auditory cortex*. Brain Res, 2006. 1073–1074: pp. 131–8.

[21] Collingridge, G.L. and T.V. Bliss, *Memories of NMDA receptors and LTP*. Trends Neurosci, 1995. 18(2): pp. 54–6.

[22] Park, P., et al., *NMDA receptor-dependent long-term potentiation comprises a family of temporally overlapping forms of synaptic plasticity that are induced by different patterns of stimulation*. Philos Trans R Soc Lond B Biol Sci, 2014. 369(1633): p. 20130131.

[23] Lauri, S.E., et al., *Presynaptic mechanisms involved in the expression of STP and LTP at CA1 synapses in the hippocampus*. Neuropharmacology, 2007. 52(1): pp. 1–11.

[24] Lauri, S.E., et al., *Functional maturation of CA1 synapses involves activity-dependent loss of tonic kainate receptor-mediated inhibition of glutamate release*. Neuron, 2006. 50(3): pp. 415–29.

[25] Klein, T., et al., *The role of heterosynaptic facilitation in long-term potentiation (LTP) of human pain sensation*. Pain, 2008. 139(3): pp. 507–19.

[26] Kirkwood, A., et al., *Modulation of long-term synaptic depression in visual cortex by acetylcholine and norepinephrine*. J Neurosci, 1999. 19(5): pp. 1599–609.

[27] Wibrand, K., et al., *Identification of genes co-upregulated with Arc during BDNF-induced long-term potentiation in adult rat dentate gyrus in vivo*. Eur J Neurosci, 2006. 23(6): pp. 1501–11.

[28] Emptage, N., T.V. Bliss, and A. Fine, *Single synaptic events evoke NMDA receptor-mediated release of calcium from internal stores in hippocampal dendritic spines*. Neuron, 1999. 22(1): pp. 115–24.

[29] Berridge, M.J., P. Lipp, and M.D. Bootman, *Signal transduction. The calcium entry pas de deux*. Science, 2000. 287(5458): pp. 1604–5.

[30] Berridge, M.J., P. Lipp, and M.D. Bootman, *The versatility and universality of calcium signalling*. Nat Rev Mol Cell Biol, 2000. 1(1): pp. 11–21.

[31] Foster, T.C., *Calcium homeostasis and modulation of synaptic plasticity in the aged brain*. Aging Cell, 2007. 6(3): pp. 319–25.

[32] Hidalgo, C. and M.A. Carrasco, *Redox control of brain calcium in health and disease*. Antioxid Redox Signal, 2011. 14(7): pp. 1203–7.

[33] Silva, A.J., et al., *CREB and memory*. Annu Rev Neurosci, 1998. 21: pp. 127–48.

[34] Hidalgo, C., et al., *Redox regulation of RyR-mediated Ca2+ release in muscle and neurons*. Biol Res, 2004. 37(4): pp. 539–52.

[35] Edwards, T.M. and N.S. Rickard, *Pharmaco-behavioural evidence indicating a complex role for ryanodine receptor calcium release channels in memory processing for a passive avoidance task*. Neurobiol Learn Mem, 2006. 86(1): pp. 1–8.

[36] Berridge, M.J., *The endoplasmic reticulum: a multifunctional signaling organelle*. Cell Calcium, 2002. 32(5–6): pp. 235–49.

[37] Fill, M. and J.A. Copello, *Ryanodine receptor calcium release channels*. Physiol Rev, 2002. 82(4): pp. 893–922.

[38] Lanner, J.T., et al., *Ryanodine receptors: structure, expression, molecular details, and function in calcium release*. Cold Spring Harb Perspect Biol, 2010. 2(11): p. a003996.

[39] Van Petegem, F., *Ryanodine receptors: structure and function*. J Biol Chem, 2012. 287(38): pp. 31624–32.

[40] Furuichi, T., et al., *Multiple types of ryanodine receptor/Ca2+ release channels are differentially expressed in rabbit brain*. J Neurosci, 1994. 14(8): pp. 4794–805.

[41] Hertle, D.N. and M.F. Yeckel, *Distribution of inositol-1,4,5-trisphosphate receptor isotypes and ryanodine receptor isotypes during maturation of the rat hippocampus*. Neuroscience, 2007. 150(3): pp. 625–38.

[42] Sharp, A.H., et al., *Differential immunohistochemical localization of inositol 1,4,5-trisphosphate- and ryanodine-sensitive Ca2+ release channels in rat brain*. J Neurosci, 1993. 13(7): pp. 3051–63.

[43] Adasme, T., et al., *Involvement of ryanodine receptors in neurotrophin-induced hippocampal synaptic plasticity and spatial memory formation*. Proc Natl Acad Sci U S A, 2011. 108(7): pp. 3029–34.

[44] Zhao, W., et al., *Spatial learning induced changes in expression of the ryanodine type II receptor in the rat hippocampus*. FASEB J, 2000. 14(2): pp. 290–300.

[45] Berridge, M.J., M.D. Bootman, and H.L. Roderick, *Calcium signalling: dynamics, homeostasis and remodelling*. Nat Rev Mol Cell Biol, 2003. 4(7): pp. 517–29.

[46] Zucchi, R. and S. Ronca-Testoni, *The sarcoplasmic reticulum Ca2+ channel/ryanodine receptor: modulation by endogenous effectors, drugs and disease states*. Pharmacol Rev, 1997. 49(1): pp. 1–51.

[47] Korkotian, E. and M. Segal, *Release of calcium from stores alters the morphology of dendritic spines in cultured hippocampal neurons*. Proc Natl Acad Sci U S A, 1999. 96(21): pp. 12068–72.

[48] Lu, Y.F. and R.D. Hawkins, *Ryanodine receptors contribute to cGMP-induced late-phase LTP and CREB phosphorylation in the hippocampus*. J Neurophysiol, 2002. 88(3): pp. 1270–8.

[49] Galeotti, N., et al., *Different involvement of type 1, 2, and 3 ryanodine receptors in memory processes*. Learn Mem, 2008. 15(5): pp. 315–23.

[50] Baker, K.D., T.M. Edwards, and N.S. Rickard, *A ryanodine receptor agonist promotes the consolidation of long-term memory in young chicks*. Behav Brain Res, 2010. 206(1): pp. 143–6.

[51] Bindokas, V.P., et al., *Superoxide production in rat hippocampal neurons: selective imaging with hydroethidine*. J Neurosci, 1996. 16(4): pp. 1324–36.

[52] Kishida, K.T., et al., *NADPH oxidase is required for NMDA receptor-dependent activation of ERK in hippocampal area CA1*. J Neurochem, 2005. 94(2): pp. 299–306.

[53] Kamsler, A. and M. Segal, *Hydrogen peroxide modulation of synaptic plasticity*. J Neurosci, 2003. 23(1): pp. 269–76.

[54] Knapp, L.T. and E. Klann, *Role of reactive oxygen species in hippocampal long-term potentiation: contributory or inhibitory?* J Neurosci Res, 2002. 70(1): pp. 1–7.

[55] Thiels, E., et al., *Impairment of long-term potentiation and associative memory in mice that overexpress extracellular superoxide dismutase*. J Neurosci, 2000. 20(20): pp. 7631–9.

[56] Tejada-Simon, M.V., et al., *Synaptic localization of a functional NADPH oxidase in the mouse hippocampus*. Mol Cell Neurosci, 2005. 29(1): pp. 97–106.

[57] Babior, B.M., *NADPH oxidase*. Curr Opin Immunol, 2004. 16(1): pp. 42–7.

[58] Cross, A.R. and A.W. Segal, *The NADPH oxidase of professional phagocytes – prototype of the NOX electron transport chain systems*. Biochim Biophys Acta, 2004. 1657(1): pp. 1–22.

[59] Hu, D., E. Klann, and E. Thiels, *Superoxide dismutase and hippocampal function: age and isozyme matter*. Antioxid Redox Signal, 2007. 9(2): pp. 201–10.

[60] Klann, E., *Cell-permeable scavengers of superoxide prevent long-term potentiation in hippocampal area CA1*. J Neurophysiol, 1998. 80(1): pp. 452–7.

[61] Serrano, F. and E. Klann, *Reactive oxygen species and synaptic plasticity in the aging hippocampus*. Ageing Res Rev, 2004. 3(4): pp. 431–43.

[62] Knapp, L.T. and E. Klann, *Potentiation of hippocampal synaptic transmission by superoxide requires the oxidative activation of protein kinase C*. J Neurosci, 2002. 22(3): pp. 674–83.

[63] Kanterewicz, B.I., L.T. Knapp, and E. Klann, *Stimulation of p42 and p44 mitogen-activated protein kinases by reactive oxygen species and nitric oxide in hippocampus*. J Neurochem, 1998. 70(3): pp. 1009–16.

[64] Lee, K. and W.J. Esselman, *Inhibition of PTPs by H(2)O(2) regulates the activation of distinct MAPK pathways*. Free Radic Biol Med, 2002. 33(8): pp. 1121–32.

[65] Palumbo, E.J., et al., *Oxidation-induced persistent activation of protein kinase C in hippocampal homogenates*. Biochem Biophys Res Commun, 1992. 187(3): pp. 1439–45.

[66] Klann, E. and E. Thiels, *Modulation of protein kinases and protein phosphatases by reactive oxygen species: implications for hippocampal synaptic plasticity*. Prog Neuropsychopharmacol Biol Psychiatry, 1999. 23(3): pp. 359–76.

[67] Kemmerling, U., et al., *Calcium release by ryanodine receptors mediates hydrogen peroxide-induced activation of ERK and CREB phosphorylation in N2a cells and hippocampal neurons*. Cell Calcium, 2007. 41(5): pp. 491–502.

[68] Kamsler, A. and M. Segal, *Paradoxical actions of hydrogen peroxide on long-term potentiation in transgenic superoxide dismutase-1 mice*. J Neurosci, 2003. 23(32): pp. 10359–67.

[69] Yermolaieva, O., et al., *Reactive oxygen species and nitric oxide mediate plasticity of neuronal calcium signaling*. Proc Natl Acad Sci U S A, 2000. 97(1): pp. 448–53.

[70] Thannickal, V.J. and B.L. Fanburg, *Reactive oxygen species in cell signaling*. Am J Physiol Lung Cell Mol Physiol, 2000. 279(6): pp. L1005-28.

[71] Munoz, P., et al., *Iron mediates N-methyl-D-aspartate receptor-dependent stimulation of calcium-induced pathways and hippocampal synaptic plasticity*. J Biol Chem, 2011. 286(15): pp. 13382–92.

[72] Munoz, P., et al., *Effect of iron on the activation of the MAPK/ERK pathway in PC12 neuroblastoma cells*. Biol Res, 2006. 39(1): pp. 189–90.

[73] McEchron, M.D. and M.D. Paronish, *Perinatal nutritional iron deficiency reduces hippocampal synaptic transmission but does not impair short- or long-term synaptic plasticity*. Nutr Neurosci, 2005. 8(5–6): pp. 277–85.

[74] Jorgenson, L.A., et al., *Fetal iron deficiency disrupts the maturation of synaptic function and efficacy in area CA1 of the developing rat hippocampus*. Hippocampus, 2005. 15(8): pp. 1094–102.

[75] Jorgenson, L.A., J.D. Wobken, and M.K. Georgieff, *Perinatal iron deficiency alters apical dendritic growth in hippocampal CA1 pyramidal neurons*. Dev Neurosci, 2003. 25(6): pp. 412–20.

[76] Harman, D., *Aging: a theory based on free radical and radiation chemistry*. J Gerontol, 1956. 11(3): pp. 298–300.

[77] Harman, D., *The biologic clock: the mitochondria?* J Am Geriatr Soc, 1972. 20(4): pp. 145–7.

[78] Droge, W., *Oxidative stress and aging*. Adv Exp Med Biol, 2003. 543: pp. 191–200.

[79] Jovanovic, Z. and S. Jovanovic, *[Resistance of nerve cells to oxidative injury]*. Med Pregl, 2011. 64(7–8): pp. 386–91.

[80] Orr, W.C. and R.S. Sohal, *Extension of life-span by overexpression of superoxide dismutase and catalase in Drosophila melanogaster*. Science, 1994. 263(5150): pp. 1128–30.

[81] Larsen, P.L., *Aging and resistance to oxidative damage in Caenorhabditis elegans*. Proc Natl Acad Sci U S A, 1993. 90(19): pp. 8905–9.

[82] Huang, T.T., et al., *Ubiquitous overexpression of CuZn superoxide dismutase does not extend life span in mice*. J Gerontol A Biol Sci Med Sci, 2000. 55(1): pp. B5–9.

[83] Tong, J., et al., *Do glutathione levels decline in aging human brain?* Free Radic Biol Med, 2016. 93: pp. 110–117.

[84] Mazzetti, A.P., et al., *Glutathione transferases and neurodegenerative diseases*. Neurochem Int, 2015. 82: pp. 10–8.

[85] Bodhinathan, K., A. Kumar, and T.C. Foster, *Redox sensitive calcium stores underlie enhanced after hyperpolarization of aged neurons: role for ryanodine receptor mediated calcium signaling*. J Neurophysiol, 2010. 104(5): pp. 2586–93.

[86] Bodhinathan, K., A. Kumar, and T.C. Foster, *Intracellular redox state alters NMDA receptor response during aging through Ca2+/calmodulin-dependent protein kinase II*. J Neurosci, 2010. 30(5): pp. 1914–24.

[87] Ghosh, D., et al., *A reversible early oxidized redox state that precedes macromolecular ROS damage in aging nontransgenic and 3xTg-AD mouse neurons*. J Neurosci, 2012. 32(17): pp. 5821–32.

[88] Haxaire, C., et al., *Reversal of age-related oxidative stress prevents hippocampal synaptic plasticity deficits by protecting D-serine-dependent NMDA receptor activation*. Aging Cell, 2012. 11(2): pp. 336–44.

[89] Lee, W.H., et al., *Role of antioxidant enzymes in redox regulation of N-methyl-D-aspartate receptor function and memory in middle-aged rats*. Neurobiol Aging, 2014. 35(6): pp. 1459–68.

[90] Robillard, J.M., et al., *Glutathione restores the mechanism of synaptic plasticity in aged mice to that of the adult*. PLoS One, 2011. 6(5): pp. e20676.

[91] Salmon, A.B., A. Richardson, and V.I. Perez, *Update on the oxidative stress theory of aging: does oxidative stress play a role in aging or healthy aging?* Free Radic Biol Med, 2010. 48(5): pp. 642–55.

[92] Belrose, J.C., et al., *Loss of glutathione homeostasis associated with neuronal senescence facilitates TRPM2 channel activation in cultured hippocampal pyramidal neurons*. Mol Brain, 2012. 5: pp. 11.

[93] Foster, T.C., *Dissecting the age-related decline on spatial learning and memory tasks in rodent models: N-methyl-D-aspartate receptors and voltage-dependent Ca2+ channels in senescent synaptic plasticity*. Prog Neurobiol, 2012. 96(3): pp. 283–303.

[94] Albert, M.S., *The ageing brain: normal and abnormal memory*. Philos Trans R Soc Lond B Biol Sci, 1997. 352(1362): pp. 1703–9.

[95] Yankner, B.A., T. Lu, and P. Loerch, *The aging brain*. Annu Rev Pathol, 2008. 3: pp. 41–66.

[96] Burke, S.N., et al., *Pattern separation deficits may contribute to age-associated recognition impairments*. Behav Neurosci, 2010. 124(5): pp. 559–73.

[97] Bergado, J.A., et al., *Spatial and emotional memory in aged rats: a behavioral-statistical analysis*. Neuroscience, 2011. 172: pp. 256–69.

[98] Foster, T.C., R.A. Defazio, and J.L. Bizon, *Characterizing cognitive aging of spatial and contextual memory in animal models*. Front Aging Neurosci, 2012. 4: p. 12.

[99] Burke, S.N. and C.A. Barnes, *Neural plasticity in the ageing brain*. Nat Rev Neurosci, 2006. 7(1): pp. 30–40.

[100] Morris, R., *Developments of a water-maze procedure for studying spatial learning in the rat*. J Neurosci Methods, 1984. 11(1): pp. 47–60.

[101] Rapp, P.R., R.A. Rosenberg, and M. Gallagher, *An evaluation of spatial information processing in aged rats*. Behav Neurosci, 1987. 101(1): pp. 3–12.

[102] Veng, L.M. and M.D. Browning, *Regionally selective alterations in expression of the alpha(1D) subunit (Ca(v)1.3) of L-type calcium channels in the hippocampus of aged rats*. Brain Res Mol Brain Res, 2002. 107(2): pp. 120–7.

[103] Agster, K.L. and R.D. Burwell, *Hippocampal and subicular efferents and afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat*. Behav Brain Res, 2013. 254: pp. 50–64.

[104] Rapp, P.R., et al., *Neuron number in the parahippocampal region is preserved in aged rats with spatial learning deficits*. Cereb Cortex, 2002. 12(11): pp. 1171–9.

[105] Thibault, O. and P.W. Landfield, *Increase in single L-type calcium channels in hippocampal neurons during aging*. Science, 1996. 272(5264): pp. 1017–20.

[106] Monti, B., C. Berteotti, and A. Contestabile, *Dysregulation of memory-related proteins in the hippocampus of aged rats and their relation with cognitive impairment*. Hippocampus, 2005. 15(8): pp. 1041–9.

[107] Moyer, J.R., Jr., et al., *Aging-related changes in calcium-binding proteins in rat perirhinal cortex*. Neurobiol Aging, 2011. 32(9): pp. 1693–706.

[108] Bruno, A.M., et al., *Altered ryanodine receptor expression in mild cognitive impairment and Alzheimer's disease*. Neurobiol Aging, 2012. 33(5): p.p 1001 e1–6.

[109] Segal, M. and E. Korkotian, *Endoplasmic reticulum calcium stores in dendritic spines*. Front Neuroanat, 2014. 8: pp. 64.

[110] Kumar, A. and T.C. Foster, *Intracellular calcium stores contribute to increased susceptibility to LTD induction during aging*. Brain Res, 2005. 1031(1): pp. 125–8.

[111] Gant, J.C., et al., *Early and simultaneous emergence of multiple hippocampal biomarkers of aging is mediated by Ca2+-induced Ca2+ release*. J Neurosci, 2006. 26(13): pp. 3482–90.

[112] Citri, A. and R.C. Malenka, *Synaptic plasticity: multiple forms, functions, and mechanisms*. Neuropsychopharmacology, 2008. 33(1): pp. 18–41.

[113] Kumar, A., K. Bodhinathan, and T.C. Foster, *Susceptibility to calcium dysregulation during brain aging*. Front Aging Neurosci, 2009. 1: p. 2.

[114] Kumar, A. and T.C. Foster, *Linking redox regulation of NMDAR synaptic function to cognitive decline during aging*. J Neurosci, 2013. 33(40): pp. 15710–5.

[115] Thibault, O., J.C. Gant, and P.W. Landfield, *Expansion of the calcium hypothesis of brain aging and Alzheimer's disease: minding the store*. Aging Cell, 2007. 6(3): pp. 307–17.

[116] Tombaugh, G.C., W.B. Rowe, and G.M. Rose, *The slow afterhyperpolarization in hippocampal CA1 neurons covaries with spatial learning ability in aged Fisher 344 rats*. J Neurosci, 2005. 25(10): pp. 2609–16.

[117] Matthews, E.A., J.M. Linardakis, and J.F. Disterhoft, *The fast and slow afterhyperpolarizations are differentially modulated in hippocampal neurons by aging and learning*. J Neurosci, 2009. 29(15): pp. 4750–5.

[118] Power, J.M., et al., *Age-related enhancement of the slow outward calcium-activated potassium current in hippocampal CA1 pyramidal neurons in vitro*. J Neurosci, 2002. 22(16): pp. 7234–43.

[119] Kumar, A. and T.C. Foster, *Enhanced long-term potentiation during aging is masked by processes involving intracellular calcium stores*. J Neurophysiol, 2004. 91(6): pp. 2437–44.

[120] Bull, R., et al., *Ischemia enhances activation by Ca2+ and redox modification of ryanodine receptor channels from rat brain cortex*. J Neurosci, 2008. 28(38): pp. 9463–72.

[121] Eager, K.R. and A.F. Dulhunty, *Activation of the cardiac ryanodine receptor by sulfhydryl oxidation is modified by Mg2+ and ATP*. J Membr Biol, 1998. 163(1): pp. 9–18.



IntechOpen

IntechOpen