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Alteration in NMDA receptor mediated glutamatergic neurotransmission in the hippocampus during senescence

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Abstract

Glutamate is the primary excitatory neurotransmitter in neurons and glia. *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors are major ionotropic glutamate receptors. Glutamatergic neurotransmission is strongly linked with Ca^{2+} homeostasis. Research has provided ample evidence that brain aging is associated with altered glutamatergic neurotransmission and Ca^{2+} dysregulation. Much of the work has focused on the hippocampus, a brain region critically involved in learning and memory, which is particularly susceptible to dysfunction during senescence. The current review examines Ca^{2+} regulation with a focus on the NMDA receptors in the hippocampus. Integrating the knowledge of the complexity of age-related alterations in Ca^{2+} homeostasis and NMDA receptor-mediated glutamatergic neurotransmission will positively shape the development of highly effective therapeutics to treat brain disorders including cognitive impairment.

Keywords

Aging; calcium homeostasis; hippocampus; glutamatergic neurotransmission; N-methyl-D-aspartate receptor; synaptic function; LTP and LTD

Introduction

The hypothesized role of senescent glutamatergic synapses in age-related memory decline is founded on studies examining the mechanisms for age-related changes in calcium (Ca^{2+})-dependent synaptic plasticity. The current review focuses on assessing age-associated changes in Ca^{2+} regulation and N-methyl-D-aspartate (NMDA) receptor-mediated synaptic transmission, in the hippocampus. In particular, we focus on possible mechanisms for an age-related decline in the function of NMDA glutamate receptors. The activity of NMDA receptors is critical for synaptic plasticity, long-term potentiation (LTP), and long-term depression (LTD), in the hippocampus.

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An age-related shift in synaptic plasticity

LTP is a rapid and long lasting increase in synaptic transmission in response to intense synaptic activity. The induction of LTP requires activation of postsynaptic NMDA receptors resulting in a large, yet brief, influx of Ca^{2+} through the NMDA receptor channel. In turn, this large rise in intracellular Ca^{2+} activates Ca^{2+} sensitive kinases. Kinase activity increases the strength of the synaptic response through phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors, which leads to insertion of additional AMPA-glutamate channels into the post-synaptic membrane [1]. Early studies demonstrated that decay of LTP increased in aged animals and correlated with forgetting, suggesting that impaired acquisition and retention of information were related to impairment in the induction and maintenance of LTP [2].

In contrast to LTP, which requires a brief but large increase in intracellular Ca^{2+}, LTD is induced by a modest and prolonged rise in intracellular Ca^{2+}. The small and sustained rise in Ca^{2+} activates Ca^{2+}-sensitive phosphatases that decrease synaptic transmission through dephosphorylation of AMPA-glutamate receptors, resulting in their removal from the post-synaptic membrane [3]. Initial studies of LTD indicated developmental regulation, such that the ability to induce LTD in the hippocampus declined from neonatal to adult periods. Thus, the discovery that aged animals exhibit increase in susceptibility to induction of LTD was unexpected [4–7]. The increase in susceptibility to LTD was shown to contribute to the decay of LTP and the induction or magnitude of LTD correlated with increased forgetting in older animals [7–9]. The results implicate LTD as a mechanism for enhancing the decay of LTP and an increased level of forgetting observed with advanced age.

The shift in synaptic plasticity during aging, favoring LTD over LTP, likely contributes to other correlates of cognitive aging including a decrease in synaptic strength and reduced transmission through the hippocampus of older animals [8,9]. In turn, the weakening of synaptic transmission could contribute to the decrease in activation of the hippocampus of aging-memory impaired humans, recorded as a decrease in the functional magnetic resonance imaging (fMRI) blood oxygen-level dependent (BOLD) signal during learning or recall [10]. Moreover, LTD is involved in synapse removal, such that LTD may decrease synaptic connectivity and contribute to the reduction in hippocampal volume [11–13]. Together, these results point to Ca^{2+} dysregulation as a mechanism for senescent physiology characterized by decreased LTP, increased LTD, and decreased synaptic transmission.

Ca^{2+}-dysregulation with advance age

Thirty years ago, observations of age-related changes in how neurons handle Ca^{2+} led to the formulation of the Ca^{2+} hypothesis of brain aging [14]. The initial Ca^{2+} hypothesis proposed that a small and prolonged increase in Ca^{2+} would over time, have toxic effects, resulting in neuronal death, similar to that observed following a large increase over a short period. Initial studies provided an evidence for a small and sustained upsurge in intracellular free Ca^{2+} with advance age [15]. Due to the discoveries that normal aging is not associated with a loss of neurons [16,17], the hypothesis has changed to reflect altered Ca^{2+}-dependent physiology, including senescent synaptic function [8,18,19].

The Ca^{2+} ion is a central signaling molecule in numerous cellular functions including apoptosis, energy production, gene regulation, cell proliferation, membrane excitability, synaptic transmission, and plasticity. Due to the ubiquitous nature of Ca^{2+} signaling, Ca^{2+} is one of the most highly regulated ions with the concentration inside the cell maintained at a level 10,000 times lower than the concentration in the extracellular space [20–22]. Accordingly, any change in Ca^{2+} regulating mechanisms can result in an alteration in cell function. Age related changes have been reported for Ca^{2+}-buffering and extrusion mechanisms [23–25]. In addition, aging hippocampal neurons exhibit a shift in the sources of Ca^{2+}. Moreover, the shift in level of different Ca^{2+} sources likely results in changes in the subcellular localization of Ca^{2+} at the synapse, dendrite, and soma. During neural activity, intracellular Ca^{2+} rises at the synapse mainly due to influx of Ca^{2+} into the cell through NMDA receptors. In the soma and dendrites, Ca^{2+} signals arise due to receptor activity; however, much of the Ca^{2+} arises from voltage-dependent Ca^{2+} channels (VDCCs) and release of Ca^{2+} from intercellular Ca^{2+} stores (ICS). In the case of aging, Ca^{2+} from NMDA receptors appears to decrease and that from VDCCs and ICS increases (Fig 1).

The NMDA Receptor

NMDA receptors represent one of the ligand-gated non-selective cation ionotropic glutamate receptors, which are present in high density within the hippocampus and play pivotal physiological and pathophysiological roles in the central nervous system [26–28]. NMDA receptors are hetero-tetrameric protein complexes composed of two classes of related subunits from seven homologous genes, GluN1, GluN2A-GluN2D, and GluN3A-GluN3B [29–36]. The majority of NMDA receptors are assemblies of two GluN1 subunits, the ubiquitously expressed and obligatory subunit, and two GluN2A-D subunits, a modulatory subunit. In addition, GluN3 subunits (GluN3A and GluN3B), without involving GluN2 subunits, can assemble with GluN1 subunits to form functional receptors [35,37–40]. Developmentally, the expression of GluN1, GluN2B, and GluN3A decreases with age compared to adulthood, while an increase in the expression of GluN2A and GluN3B is reported during development [40].

NMDA receptors, along with AMPA and kainite receptors, are critical for the rapid regulation of synaptic plasticity including LTP and LTD, which are important cellular correlates for learning and memory function [41–47]. The induction of LTP and LTD involves activation of NMDA receptors, Ca^{2+} entry, and differential activation of kinases/phosphatases [18]. Interestingly, recent work indicates that amyloid beta could act on GluN2B subunits, through metabotropic mechanisms, to influence phosphatase/kinase activity, influencing synaptic function and spine loss [48,49].

Physiological studies consistently indicate that NMDA receptor mediated excitatory postsynaptic potentials in the Schaffer collateral pathway of the hippocampus are reduced by approximately 50–60% in aged animals [50–57]. In turn, a decrease in NMDA receptor function is likely to influence induction of AMPA receptor mediated synaptic plasticity [48,58] (i.e. metaplasticity [59]).

Expression of NMDA receptor during aging

Alteration in expression of specific NMDA receptor subunits might be a potential mechanism for the observed decrease in the NMDA receptor function [60]. GluN1 subunit of NMDA receptor is highly expressed in the hippocampus; results demonstrate that GluN1 subunit is susceptible to aging process. A significant decrease in the expression of GluN1 protein levels with advancing age is observed in the hippocampus [51,61–65]. GluN1 mRNA expression of GluN1 subunit also declines with increasing age in the hippocampus [60,66]. In contrast, other studies report modest or no age-related decrease in GluN1 protein expression in the whole hippocampus [67,68]. These studies suggest that the GluN1 subunit of the NMDA receptor is variably susceptible to the influence of aging process.

The GluN2B subunit is highly expressed throughout the brain during early stages of development and declines at the onset of sexual maturity; GluN2A subunit-containing NMDA receptors increase across the same life span [69–74]. A shift in GluN2A and GluN2B expression in the hippocampus is thought to contribute to developmental changes in cognition and synaptic function [75]. GluN2A subunit of NMDA receptor is highly expressed in the hippocampus and other brain regions. Aging is associated with no change or a modest decrease in the expression of GluN2A mRNA expression in the hippocampus [60,76,77]. Similarly, there is some indication that expression of GluN2A protein is decreased in the hippocampus of aged animals when compared with middle aged animals [63], while other studies indicate no age-related change in the GluN2A subunit in the hippocampus [62,78,79].

Interestingly, GluN2B subunits of NMDA receptor display slower channel kinetics and greater Ca^{2+} conductance. These channels, by taking longer duration to close, allow more Ca^{2+} influx into the cell over a longer period, and are therefore thought to be more conducive to the induction of activity dependent synaptic plasticity. Additionally, upregulation of GluN2B significantly augments LTP and memory function in rodents [80,81], including aged mice [82]. Finally, studies that involve viral vector-mediated upregulation of GluN2B expression in adult hippocampus suggest that increasing the level of GluN2B expression can improve cognitive function during aging [54,79].

In contrast to GluN2A, expression of GluN2B protein [62–64, 67, 68, 78, 83, 84] and GluN2B mRNA [60, 76–78, 83, 85] is generally reported to decline in the hippocampus with advanced age. One problem is that few studies have examined the expression of both subunits in the same animal. For studies that examine the protein expression of both subunits, some studies suggest that decreased expression, mainly of GluN2B, increases the ratio of GluN2A/GluN2B protein in several brain regions [62, 78, 86]. However, other reports indicate that both subunits decline equally with advanced age [63, 67].

Modification of existing receptors

In addition, to the required binding of glutamate and postsynaptic depolarization, NMDA receptors are regulated by posttranslational modification of the receptor. In adults, the NMDA receptor synaptic responses can undergo LTP (NMDAR-LTP) and LTD (NMDAR-LTD) [87]. NMDAR-LTP depends on the activity of NMDARs, a subsequent increase in

intracellular Ca^{2+}, and kinase activity [88–90]. Activation of kinases, such as tyrosine kinase [91, 92], protein kinase C (PKC) [93, 94], protein kinase A [95], and CAMKII increases NMDA receptor mediated currents. Interestingly, aging is associated with a shift in the balance of kinase/phosphatase activity, favoring an increase in the phosphatase activity [96–98].

With advancing age, the cellular localization, basal or stimulation induced activity may be altered [53, 99]. In contrast to kinases, the activity of protein phosphatase appears to be augmented with normal aging, influencing synaptic function [96, 97, 100]. Protein phosphatases, including calcineurin and protein phosphatase 1, decrease NMDA receptor currents [92, 95, 101]. Phosphorylation state of GluN1, GluN2A or GluN2B subunits can rapidly regulate surface expression and localization of the NMDA receptors [102–105]. Inhibition of phosphatase activity increases the AMPA receptor component of synaptic [97] transmission, specifically in aged animals[97] .The increase in synaptic transmission due to phosphatase inhibition may be linked to increased susceptibility to induction of LTD and thus, represent reversal of LTD. Inhibition of phosphatase activity also increases NMDA receptor-mediated synaptic transmission in aged animals; however, the increase is relatively small relative to the decrease in the NMDA synaptic response associated with aging [53].

Recent work suggests that redox regulation of NMDA receptor function contributes to schizophrenia (Steullet et al., 2016), stressor-induced depressive-like behavior (Ibi et al., 2017), and synaptic plasticity during development [106]. In young animals, NMDA receptor function is modulated by redox state, such that under oxidizing conditions, disulfide bonds can form between cysteine residues in the NMDA receptor subunits [107–109]. Three pairs of cysteine residues are located within the N-terminal regulatory domain of the receptor (two pairs reside in GluN1 and one pair resides in GluN2A subunit) [108, 110, 111]. The formation of disulfide bonds between cysteine residues is thought to decrease the current through the NMDA receptor. In contrast to younger animals, little or no effect of oxidizing agents was observed for older animals, suggesting that cells were already in an oxidized state. In contrast, reducing conditions enhanced NMDA receptor mediated synaptic responses in hippocampus of aged animals [53, 55, 56, 112–114]. Recent results provide evidence for a link between the redox-mediated decline in NMDA receptor function and the emergence of an age-related cognitive phenotype with impairment in the rapid acquisition and retention of novel spatial information [55, 56]. These results demonstrate that the age-related decrease in NMDA receptor-mediated synaptic responses at CA3-CA1 hippocampal synapses with advanced age is related to redox state such that the reducing agent, dithiothreitol (DTT) significantly enhanced the NMDA receptor component of the synaptic response to a greater extent in cognitively impaired animals relative to unimpaired animals [55] (Fig 2).

The mechanism for redox regulation of NMDA receptor function is unclear. An age-related shift in the composition of NMDA receptor subunits could render the NMDA receptor more susceptible to redox regulation. As noted above, the GluN2A subunit has unique extracellular cysteine residues, and reducing the extracellular disulfide bonds, by the addition of extracellular glutathione, increases the NMDA receptor response of diheteromeric GluN1-GluN2A receptors [115]. However, in the case of aging, addition of

extracellular glutathione and other antioxidants that do not readily pass the cell membrane do not increase the NMDA receptor response in aged animals [53, 116]. Rather, intracellular application of glutathione increased the NMDA receptor response demonstrating an important role for intracellular redox state [53]. Furthermore, the DTT-mediated growth of the NMDA receptor response depends on the activity of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [53]. Interestingly, NMDAR-LTP is sensitive to redox conditions, [117, 118] and is impaired in aged animals [79], suggesting that redox mechanisms may underlie an age-related decrease in NMDAR-LTP.

Modification of NMDA receptor function by agonist

In addition to binding glutamate, glycine acts as a co-agonist, binding to the GluN1 subunits. D-serine might represent another physiological co-agonist of the NMDA receptor as it can bind at the glycine-binding site [119–123]. D-serine acts as a neuronal signaling molecule leading to upregulation of NMDA receptors. In addition, D-serine is highly expressed in the brain and released from astrocytes [120, 124–127]. D-serine is required for NMDA receptor activation, and may have preferential affinity/effectiveness for NMDA receptors that contain GluN2B subunits [121]. The levels of D-serine are dramatically reduced with advanced age [128–130]. One possibility is a loss of the serine racemase enzyme, which generates D-serine from L-serine [131, 132]. A decline in serine racemase mRNA is observed in the hippocampus of aged rats [130]. The enzyme serine racemase generates D-serine from L-serine; pharmacological or viral gene delivery tools could be employed to increase endogenous levels of D-serine or serine racemase expression. Future studies to upregulate the expression of serine racemase, in order to enhance the endogenous level of D-serine, could provide another avenue to restore impaired NMDA receptor function during aging and under pathological conditions.

Influence of VDCCs and ICS on NMDA receptor function

In addition to binding of the transmitter glutamate, NMDA receptor activation requires postsynaptic depolarization to relieve the Mg^{2+} block of the channel. For CA1 neurons from aged animals, depolarization induced by a burst of afferent activity is reduced, due to activation of Ca^{2+}-dependent K^+ channels. The augmentation in the afterhyperpolarization (AHP) amplitude diminishes the activation of NMDA channels, further contributing to impaired synaptic plasticity [18, 19]. The enhanced AHP with age is linked to increased involvement of VDCCs and internal Ca^{2+} stores [112, 133–147]. Thus, changes in Ca^{2+} from VDCCs or ICS can act through the AHP to impair NMDA receptor function.

VDCCs are ion channels in the plasma membrane open in response to membrane depolarization and allow Ca^{2+} influx into the cell from the extracellular space. In hippocampal CA1 pyramidal neurons of the rat, the L-type Ca^{2+} currents are increased [148, 149] and an increase in the density of functional L-type VDCCs have been reported for aged animals [150]. The idea that L-channels are increased in the hippocampus during senescence is also supported by mRNA and protein expression studies indicating an increase in $Ca_V1.3$ [151–153]. Treatments to reduce the AHP permits increase activation of NMDA receptor, to shift the threshold for induction of synaptic plasticity [154, 155]. In aged rats, under L-channel blockade, the induction of LTP is facilitated for low level synaptic activation, which

would not induce synaptic modification in young animals [154]. It should be noted that L-channel blockade does not completely ameliorate age-related differences. The AHP amplitude is reduced but not to the levels observed in young animals [112, 146].

In addition to Ca^{2+} influx from outside the cell, ICS play a major role in regulating larger Ca^{2+} signals [156, 157]. Organelles, including the endoplasmic reticulum, mitochondria, and lysosomes act as Ca^{2+} buffering systems - releasing and sequestering Ca^{2+} [158–164]. Thus, there are at least two possible mechanisms by which ICS can regulate Ca^{2+} homeostasis: 1) release of stored Ca^{2+} to enhance Ca^{2+} signals and 2) removing cytosolic Ca^{2+} following a large influx.

Two pathways control the release of Ca^{2+} from the endoplasmic reticulum, Ca^{2+}-induced Ca^{2+} release (CICR) and the inositol (1,4,5)-trisphosphate (IP_3) pathway activated by G protein-coupled receptors. G protein-coupled receptors activate phospholipase C to form diacylglycerol and IP_3, which act on IP_3 receptors (IP_3Rs) to release Ca^{2+} from ICS. Previous studies have observed an age associated decrease in IP_3Rs in several brain regions [165–168]. Despite a general decrease in the receptor, the literature suggests that a decrease in IP_3 induced Ca^{2+} release is either limited to cortical cells [165] or no age-related change is observed [169]. The disconnect between a reduction in IP_3R expression and the apparent absence of an effect of age on IP_3-induced Ca^{2+} release may be due to increased oxidation of the IP_3Rs which has been demonstrated to increase IP_3R function in brain cells [170, 171]. As such, reduced expression may act as compensation for an altered redox state, in order to maintain proper IP_3 signaling.

CICR is a Ca^{2+} amplification process that is initiated by influx of Ca^{2+} through membrane channels (i.e. VDCCs) (Fig 1). The intracellular Ca^{2+} binds ryanodine receptors (RyRs) to release additional Ca^{2+} into the cytosol from the endoplasmic reticulum. Accumulating evidence supports a role of altered CICR in contributing to altered physiology of normal aging. The increased involvement of RyRs does not appear to be due to increased RyR expression [167]. Rather, an age-related increase in oxidative stress and a shift in the intracellular redox state may enhance the responsiveness of RyRs to intracellular Ca^{2+} [112, 172–174]. The redox state influences the formation of cysteine disulfide bonds. The disulfide bonds of RyR for ICS determine Ca^{2+} release and the amplitude of the AHP. In the case of NMDA receptors, redox sensitive disulfide bonds are localized to NMDA receptor subunits and to molecules such as Ca^{2+}/calmodulin-dependent protein kinase II that modify NMDA receptor function. The age-dependent specificity of oxidizing agents and DTT provide strong support for the tenet that redox stress mediates senescent physiology. Increased CICR appears to contribute to the larger AHP during aging [5, 138, 147]. As noted above, hippocampal cells exhibit increase Ca^{2+} from L-type Ca^{2+} channels, which could provide a source of Ca^{2+} to fill ICS and activate CICR from ICS.

The increase in CICR activates Ca^{2+}-dependent potassium channels in the membrane, inducing larger AHP. Attenuating CICR, by blocking RyR or depletion of Ca^{2+} from ICS, has a greater influence in reducing the amplitude of the AHP in aged animals [112, 138], indicating an aging-specific mechanism. Moreover, attenuation of CICR promotes induction of LTP and inhibits LTD during senescence [5, 138]. Thus, the relative shift in Ca^{2+} sources,

with reduced extracellular influx of Ca^{2+} from NMDA receptors and increased release of Ca^{2+} from ICS, underlies senescent physiology, which is characterized by enhanced amplitude of AHP, a decrease in NMDA voltage-gated channel activity, decreased synaptic transmission, and reduced synaptic plasticity.

Conclusion

Ideas about the role of senescent glutamatergic synapses in contributing to the age-related cognitive impairment are based on studies delineating the mechanisms for age-associated changes in Ca^{2+}-dependent synaptic plasticity. Specifically, aging associated alterations in Ca^{2+} regulation modify NMDA glutamate receptor mediated synaptic transmission including impaired LTP and enhanced LTD. In addition to altered synaptic plasticity, alterations in NMDA receptor subunit expression profile, molecular and biochemical modulatory mechanisms, and alterations in Ca^{2+} sources provide impetus for altering the NMDA receptor-mediated synaptic transmission. These altered senescent glutamatergic synaptic plasticity mechanisms contribute to cognitive aging. Due to the critical importance of NMDA glutamate receptors in synaptic transmission and cognitive function, a selective upregulation of NMDA receptor function may provide an avenue for treating age-associated cognitive deficits. Clearly, future research will need to delineate the contributions of several mechanisms in optimizing specific subunit contribution and influence of upregulation in mediating cognition. Thus, it will be imperative for future research to determine whether enhancing or inhibiting NMDA receptor function by upregulating or downregulating different subunits expression configurations will be beneficial in preserving cognitive domain and promoting successful cognitive aging.

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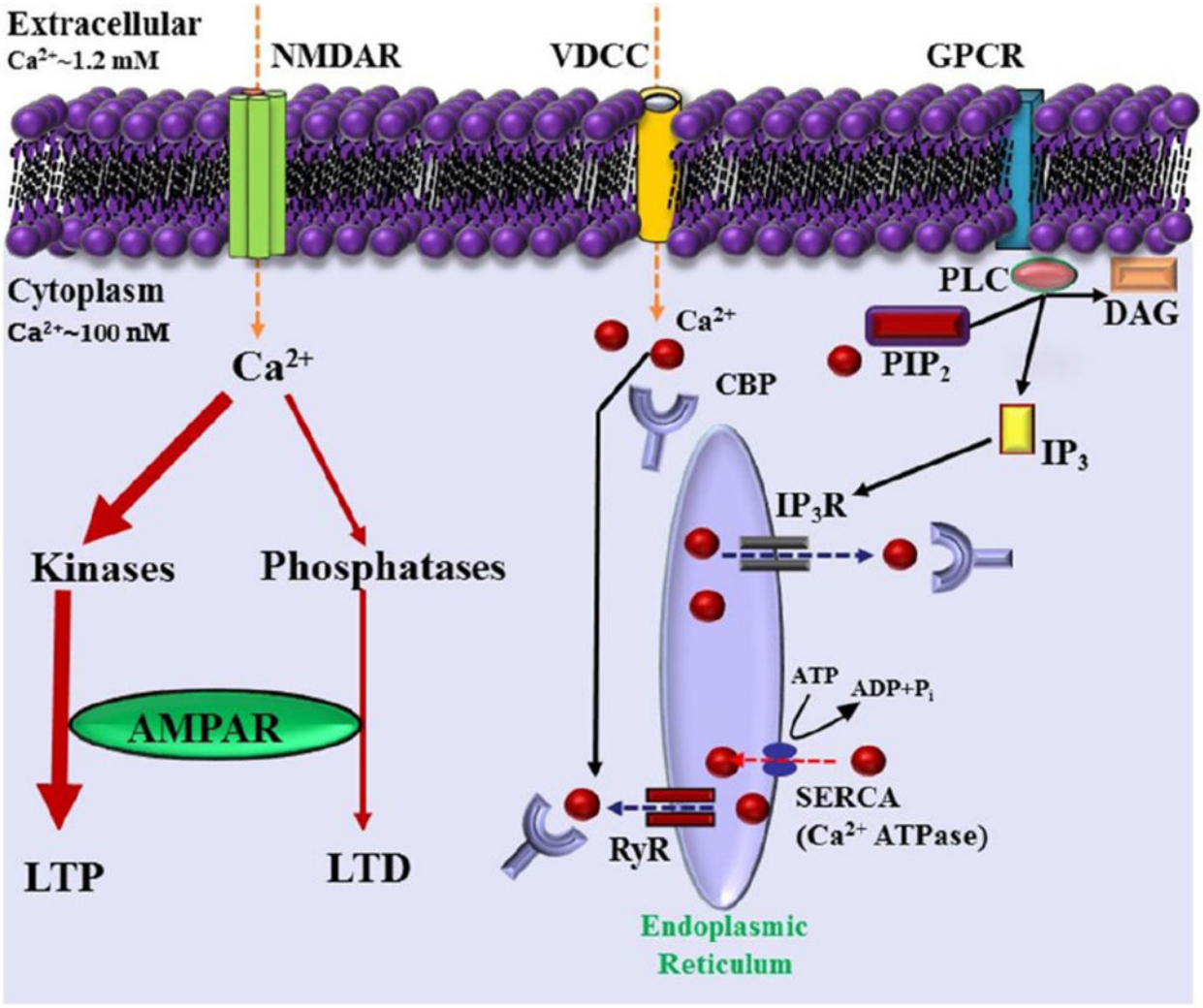

Figure 1.

Model illustrating various Ca^{2+} sources including NMDA receptor (NMDAR), voltage-dependent Ca^{2+} channels (*VDCC*), and G protein-coupled receptor (*GPCR*). Ca^{2+} (*red balls*) influxes into the cytosol (*yellow dashed arrows*) through these sources in a healthy neuron. The release of Ca^{2+} into the cytoplasm also occurs from the intracellular Ca^{2+} stores through inositol (1,4,5)-trisphosphate receptor (*IP_3R*) and ryanodine receptors (*RyR*) involving phospholipase C (PLC), diacylglycerol (DAG) and inositol (1,4,5)-trisphosphate (IP_3). Organelles, including the endoplasmic reticulum act as a Ca^{2+} buffering system, releasing and sequestering Ca^{2+}. Further, the model depicts Ca^{2+} buffering and extrusion pathways (*red dashed arrows*), involving plasma membrane Ca^{2+} ATPase, sarcoplasmic reticulum Ca^{2+} ATPases (*SERCA*), and various Ca^{2+} binding proteins (*CBP*).

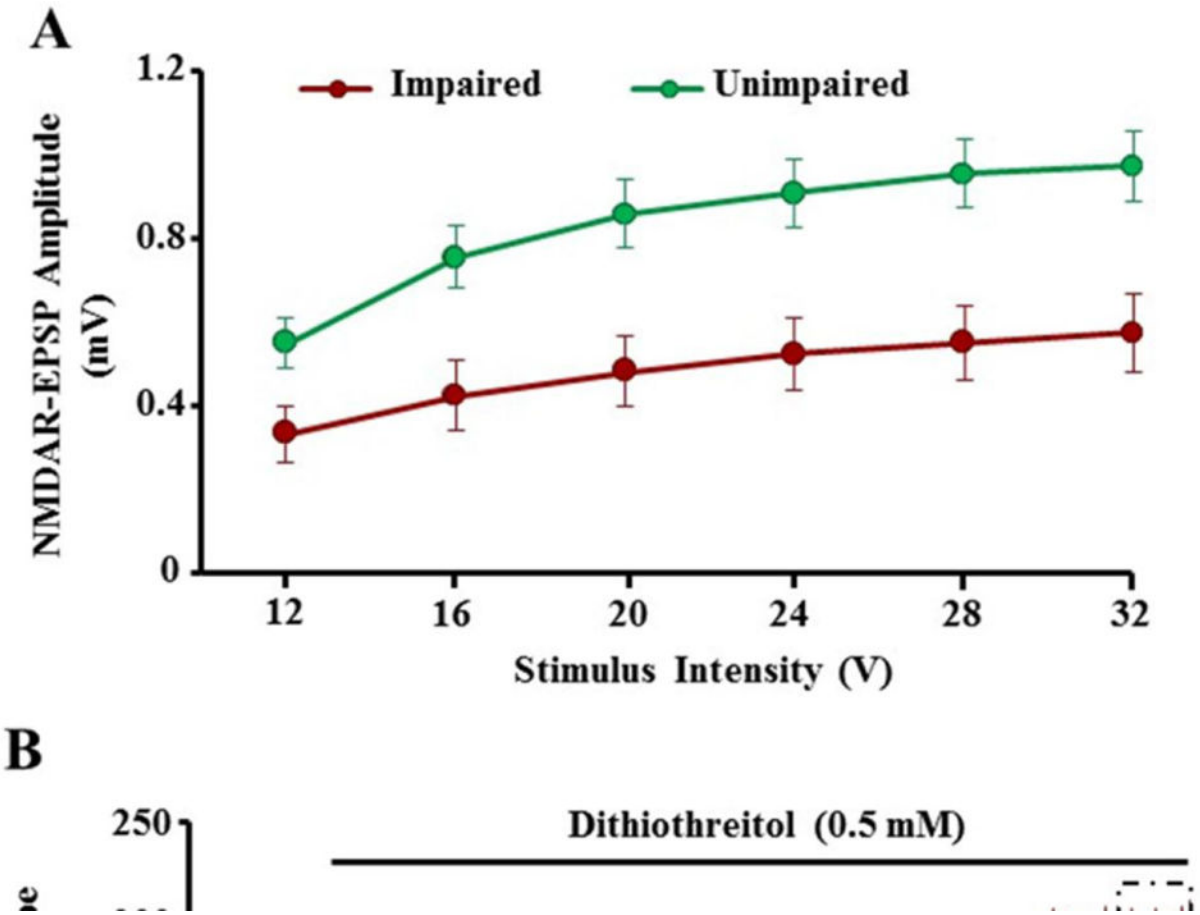

Figure 2.

Redox environment contributes to the decline in NMDA receptor function associated with cognitive impairment. **A)** Input–output curves for the mean NMDA receptor EPSP (NMDAR-EPSP) amplitude evoked by increasing stimulating voltage. **B)** Time course of changes in the slope of NMDA receptor-mediated EPSP obtained from hippocampal slices 10 min before and 60 min after bath application of the reducing agent DTT (0.5 mM, solid line) in unimpaired (red circles) and impaired (green circles) animals. **C)** Bars represent the mean ± SEM change in NMDAR-EPSP slope after the application of DTT in unimpaired (red circles) and impaired (green circles) animals. The asterisk indicates a significant increase in NMDAR-EPSP slope in impaired animals when compared with unimpaired (modified from Kumar and Foster, JNS, 2013).