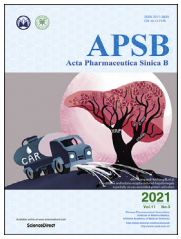
Acta Pharmaceutica Sinica B 2021;11(3):599–608

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Targeting redox-altered plasticity to reactivate synaptic function: A novel therapeutic strategy for cognitive disorder

Pei Wang[a], Fang Wang[a,b,c,d], Lan Ni[a], Pengfei Wu[a,c,*], Jianguo Chen[a,b,c,d,*]

[a]*Department of Pharmacology, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
[b]*Key Laboratory of Neurological Diseases (HUST), Ministry of Education of China, Wuhan 430030, China*
[c]*The Key Laboratory for Drug Target Researches and Pharmacodynamic Evaluation of Hubei Province, Wuhan 430030, China*
[d]*Laboratory of Neuropsychiatric Diseases, the Institute of Brain Research, Huazhong University of Science and Technology, Wuhan 430030, China*

Received 9 August 2020; received in revised form 22 September 2020; accepted 13 October 2020

KEY WORDS

Reactive oxygen species;
N-Methyl-D-aspartate receptor;
Oxidative stress;
Synaptic plasticity;
Long-term potentiation;
Cognitive disorder;
Learning and memory;

Abstract Redox-altered plasticity refers to redox-dependent reversible changes in synaptic plasticity *via* altering functions of key proteins, such as *N*-methyl-D-aspartate receptor (NMDAR). Age-related cognitive disorders includes Alzheimer's disease (AD), vascular dementia (VD), and age-associated memory impairment (AAMI). Based on the critical role of NMDAR-dependent long-term potentiation (LTP) in memory, the increase of reactive oxygen species in cognitive disorders, and the sensitivity of NMDAR to the redox status, converging lines have suggested the redox-altered NMDAR-dependent plasticity might underlie the synaptic dysfunctions associated with cognitive disorders. In this review, we summarize the involvement of redox-altered plasticity in cognitive disorders by presenting the available evidence. According to reports from our laboratory and other groups, this "redox-altered plasticity" is

Abbreviations: AAMI, age-associated memory impairment; AD, Alzheimer's disease; AMPARs, α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptors; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; DG, dentate gyrus; DTNB, 5,5-dithio-bis-2-nitrobenzoic acid; DTT, dithiothreitol; DS, Down syndrome; EPSPs, excitatory postsynaptic potentials; Glu, glutamate; GSK-3β, glycogen synthase kinase-3β; HFS, high-frequency stimulation; H_2O_2, hydrogen peroxide; LFS, low-frequency stimulation; LTP, long-term potentiation; LTD, long-term depression; MF, mossy fiber; NAC, *N*-acetyl cysteine; NADPH, nicotinamide adenine dinucleotide phosphate; NMDARs, *N*-methyl-D-aspartate receptors; NO, nitric oxide; PTM, posttranslational modification; ROS, reactive oxygen species; SC, Schaffer collateral; SNOC, *S*-nitrosocysteine; TFAM, mitochondrial transcription factor A; VD, vascular dementia.

*Corresponding authors.
E-mail addresses: chenj@mails.tjmu.edu.cn (Jianguo Chen), wupengfeihust@sina.com (Pengfei Wu).

Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2020.11.012

Hydrogen sulfide

more similar to functional changes rather than organic injuries, and strategies targeting redox-altered plasticity using pharmacological agents might reverse synaptic dysfunctions and memory abnormalities in the early stage of cognitive disorders. Targeting redox modifications for NMDARs may serve as a novel therapeutic strategy for memory deficits.

1. Introduction

Age-related cognitive disorders, such as Alzheimer's disease (AD), vascular dementia (VD), and age-associated memory impairment (AAMI), have attracted increasing attention with the accelerating trend of population aging. The prevalence rate of cognitive disorders, including mild cognitive impairment and dementia, is approximately 3%−5% for people aged 65−74 years. For the population over the age of 85, one case of dementia is observed in every three people[1]. The most important pathological feature of age-related cognitive disorders is the decline and impairment of learning and memory abilities. However, an ideal therapy to delay the progress of the age-related cognitive disorders is still unavailable. The mechanisms of learning and memory are one of the most striking subjects in the field of contemporary neurological science.

In the past forty years, researchers have revealed that the most important neurophysiological bases of memory are the activity-dependent changes in synaptic efficacy, such as long-term potentiation (LTP) and long-term depression (LTD). As early as 1949, Donald Olding Hebb, a famous Canadian psychologist, proposed Hebb's hypothesis: when a stimulus is applied to a collection of cells, cells interacting with each other might exhibit corresponding changes. The synapse is a special structure connecting neural cells that typically forms between neurons. When the presynaptic terminals are activated by a high-frequency stimulation, the efficiency of synaptic transmission may be increased. In 1973, Bliss et al.[2] were the first to show that a high-frequency stimulation (HFS) at the perforating fiber induced a significant increase in synaptic efficacy. Subsequently, the synaptic plasticity in the hippocampus, particularly LTP, has consistently been shown to be the biological basis of learning and memory[3,4]. After presynaptic depolarization which triggers neurotransmitter release to activate postsynaptic α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptors (AMPARs), depolarization is induced to remove magnesium ions from postsynaptic *N*-methyl-D-aspartate receptors (NMDARs); thus the NMDAR-dependent synaptic transmission is activated and LTP is induced. Because impairment in hippocampal LTP has been observed in various models of cognitive disorders[5−9], it may serve as a common early pathological basis for various cognitive disorders.

Oxidative stress, which results from an imbalance between antioxidant defenses and reactive oxygen species (ROS) generation, is one of the most important pathogenic factors involved in various aging-related diseases[10,11]. A high lipid content and a relatively low level of antioxidant enzymes make the brain more vulnerable to ROS[12], such as $O^{2-\bullet}$, H_2O_2, OH and $^1O_2$, which are generated by mitochondrial aerobic respiration, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine/xanthine oxidase. The function of the endogenous antioxidant system, which includes glutathione, vitamin C, carnosine, thioredoxin and superoxide dismutase, decreases with aging. In recent years, evidences from both animal models and clinical data suggest that oxidative stress may underlie the pathophysiological mechanisms of cognitive disorders[13,14]. The abnormal accumulation of ROS or oxidative products are observed in many cognitive disorders. For instance, an increase in the level of lipid peroxidation products and a decrease in antioxidants have been observed in the models of VD and AD, and particularly in patients with AAMI and AD[15]. However, its specific neurobiological mechanism remains unclear. Most studies have focused on the role of redox-induced injury in the neurodegeneration related to cognitive disorders[16−20]. Redox-induced injury refers oxidative stress-triggered cell dysfunctions that may cause neuronal cell death, such as neuronal cell apoptosis, necrosis and impaired autophagy. For instance, an increase of ROS concentration occurs during the developmental apoptotic neurons[21,22] and excessive amounts of ROS not only impairs macromolecules, but also triggers apoptotic signals, such as death receptor-mediated extrinsic pathways and mitochondria-mediated intrinsic pathways[23−26]. For the critical role of neurodegeneration in many diseases, there is increasing evidence that redox-induced injury is involved in the etiology and pathogenesis of neurodegenerative disorders. However, although neurodegeneration is involved in both AD and VD, it may occur in the late phase, but not early phase, of the cognitive disorders because it is a type of structural damage. Notably, oxidative stress not only causes cell injury but also affects the biological functions by triggering redox-dependent changes, including post-translational modifications (PTMs), protein degradation and epigenetic modifications. According to reports from our laboratory and other groups, oxidative stress impairs LTP in the hippocampus[27−35]. Furthermore, replenishing the cellular reducing ability by administering thiol agents such as dithiothreitol (DTT) and glutathione (GSH) reverses aging-associated synaptic dysfunctions[36−38]. In this manuscript, we designate this impairment in LTP as redox-altered plasticity and summarize the emerging evidence of redox-altered plasticity under pathological conditions. Different from redox-induced injury, redox-altered plasticity is caused by the redox-dependent changes in biological functions, and is more like functional changes rather than structural injuries, which may represent an ideal therapeutic window for pharmacological intervention. We propose that approaches targeting redox-altered plasticity may serve as a novel therapeutic strategy to reverse memory deficits in the early stages of cognitive disorders.

2. What is redox-altered plasticity?

Redox-altered plasticity refers to redox-dependent reversible changes in synaptic plasticity *via* altering functions of key proteins, such as NMDAR. ROS exert remarkable effects on the intracellular messenger molecules[39] and interact directly with a variety of redox-sensitive proteins *via* sulfur-containing residues

(cysteine and methionine residues) or coenzymes containing metal ions. Colton et al.[27] in 1986 showed that exposure to 1×10^{-4} mol/L hydrogen peroxide (H_2O_2) depressed synaptic transmission at the lobster neuromuscular junction. They firstly observed a blockade of LTP in the hippocampus by a microinjection of 1 mmol/L H_2O_2 and reported the phenomenon of redox-altered plasticity in 1989[28]. Then, Pellmar et al.[29] revealed that 0.002% H_2O_2 prevents the maintenance of LTP in the CA1 region of the hippocampus isolated from guinea pigs. Avshalumov et al.[30] further clarified the mechanisms underlying the H_2O_2-mediated inhibition of synaptic transmission in rat hippocampal slices, including the generation of hydroxyl radicals (·OH). These early reports indicated that high concentrations of ROS induce redox-impaired plasticity. However, beginning in the 1990s, many studies identified physiological concentrations of ROS as second messengers to facilitate redox-enhanced plasticity[40]. As shown in the study by Kamsler et al.[41], H_2O_2 (1 μmol/L) increases the amplitude of NMDAR-dependent LTP in the hippocampus. According to Knapp et al.[42], the generation of superoxide ions *in vivo* by the xanthine and xanthine oxidase system causes a sustained increase in basal synaptic transmission in the hippocampal CA1 area. Huddleston et al.[43] observed a sustained increase in basal synaptic transmission in the hippocampal CA1 area induced by a low concentration of superoxide radicals through a mechanism involving the activation of ERK and the ryanodine receptor. Second, ROS scavengers or antioxidant enzymes impede the LTP impairment. Klann et al.[44] observed a significant inhibitory effect of a superoxide ion scavenger, manganese porphyrin, on the induction of LTP. In the mice overexpressing extracellular superoxide dismutase or knocking out NADPH oxidase gp91, significant LTP and memory deficits were observed[45,46]. Recent studies have revealed another redox-impaired plasticity induced by overproduction of mitochondria-derived ROS. MitoQ, a selective mitochondrial ROS scavenger, alleviates the LTP impairment induced by amyloid β[47], and overexpression of a mitochondrial superoxide dismutase 2 produces a similar effect[48].

In the past decade, a series of studies from our laboratory confirmed that high ROS concentrations mainly impair NMDAR-dependent LTP in the hippocampus, and we were the first to show that this impairment can be prevented and even reversed by thiol agents[31–35]. In the study by Cai et al.[31], chloramine T (20 μmol/L) significantly inhibited the induction of LTP in the CA1 region of hippocampal slices *in vitro*. Additionally, a high concentration of chloramine T (20 mmol/L) noticeably attenuated LTP *in vivo*, and this inhibition was reversed by the reductant DTT[32]. In addition, we confirmed that the specific sulfhydryl oxidant 5,5-dithio-bis-2-nitrobenzoic acid (DTNB) impaired the NMDAR-dependent LTP in the hippocampus[31,33]. Interestingly, DTT or β-mercaptoethanol not only prevents the oxidant-induced impairment of LTP but also reverses the impaired LTP induced by aging *via* reversing the hypofunction of NMDA receptor[33]. Therefore, we proposed the notion of redox-altered plasticity, which has three key features. First, the redox status affects synaptic plasticity by altering protein function and signal transduction. The neurotoxic effects of strong oxidants, which might cause neuronal apoptosis and necrosis, do not appear to be involved in the redox-altered plasticity (Fig. 1). Second, redox-triggered alterations in plasticity are blocked and even reversed by reductants, such as DTT. As a reversible process, redox-altered plasticity may emerge as a window to provide interventions that will alleviate the memory impairment. Third, this alteration selectively affects synaptic plasticity *via* a postsynaptic mechanism, but not synaptic transmission itself.

3. Possible mechanisms underlying redox-altered plasticity

NMDAR plays an essential role in the induction of LTP and the acquisition of memories. The hypofunction of NMDAR is primarily responsible for deficits in synaptic plasticity in aged animals, animal models, and patients with age-related neurodegenerative diseases and other cognitive disorders[7,8,49–52]. Recent studies have identified alterations in the functional properties of NMDAR, rather than in the level of expression or density, as the cause of NMDAR hypofunction in individuals with various disorders[49,50,53,54]. The NMDAR responses delayed in aged animals, suggesting that age-related LTP and memory deficits may be due to the decrease in the NMDAR-mediated component of synaptic transmission. Age-related LTP deficits in the hippocampus generally depend on NMDAR hypofunction. According to the reports describing the regulatory effects of oxidants on NMDARs, the voltage clamp recordings from *Xenopus laevis* oocytes provide important early evidence: oxidants such as DTNB (0.5 mmol/L) inhibit NMDAR function, whereas DTT (2 mmol/L) enhances NMDAR function[55]. As shown in our previous study, the sulfhydryl oxidant DTNB (100 μmol/L) decreases the magnitude of NMDAR-mediated fEPSPs in hippocampal slices[33].

Kumar et al.[56] observed a redox-mediated decrease in NMDAR function during aging that is associated with cognitive decline. Robillard et al.[38] further reported a significant effect of *N*-acetylcysteine (NAC), a precursor molecule that increases glutathione (GSH) synthesis, on alleviating the aging-associated LTP impairment in aging rats. This finding was supported by a report showing that oral administration of a glutathione supplement to aged mice increases the L-type calcium channel-dependent LTP in aged animals to compensate for NMDAR-dependent LTP in the hippocampus[38]. In response to long-term dietary supplementation of *N*-acetyl-L-cysteine, NMDAR hypofunction caused by aging was restored by an increase in D-serine-dependent NMDAR activation in a recent study[57]. Notably, a sulfhydryl reducing agent also enhances NMDAR function through a direct interaction[55]. DTT increases the currents from NR2A-containing NMDAR, suggesting that the main redox-sensitive site of NMDAR is on the NR2A subunit[58]. The redox modification of NR2A subunits is likely to be an important target for drug interventions for aging-related cognitive disorders. However, direct evidence elucidating the precise changes in the redox status of the NR2A subunit in individuals with cognitive disorders is not available.

In addition to NMDAR, other targets may also be involved in the redox-dependent regulation of synaptic plasticity. Silva et al.[59] discovered that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) mutant mice exhibited an intact NMDAR function but a significant deficiency in LTP. According to Bodhinathan et al.[60], the mechanisms underlying the age-dependent redox modulation of NMDARs are mediated by redox-triggered CaMKII inactivation. As shown in the study by Yang et al.[32], an intracerebroventricular injection of 20 mmol/L Ch-T inhibits the phosphorylation of CaMKII during the induction of LTP in the rat dentate gyrus (DG). Maalouf et al.[36] observed an important role for protein phosphatase 2A (PP2A) overactivation in the H_2O_2-induced impairment of LTP, which leads to the dephosphorylation and inactivation of CaMKII. LTP is also impaired in transgenic mice conditionally overexpressing glycogen synthase kinase-3β (GSK-3β), a serine/threonine protein kinase. GSK-3β mediates oxidative stress-induced neuronal injury[61]. In addition, Cai et al.[31]

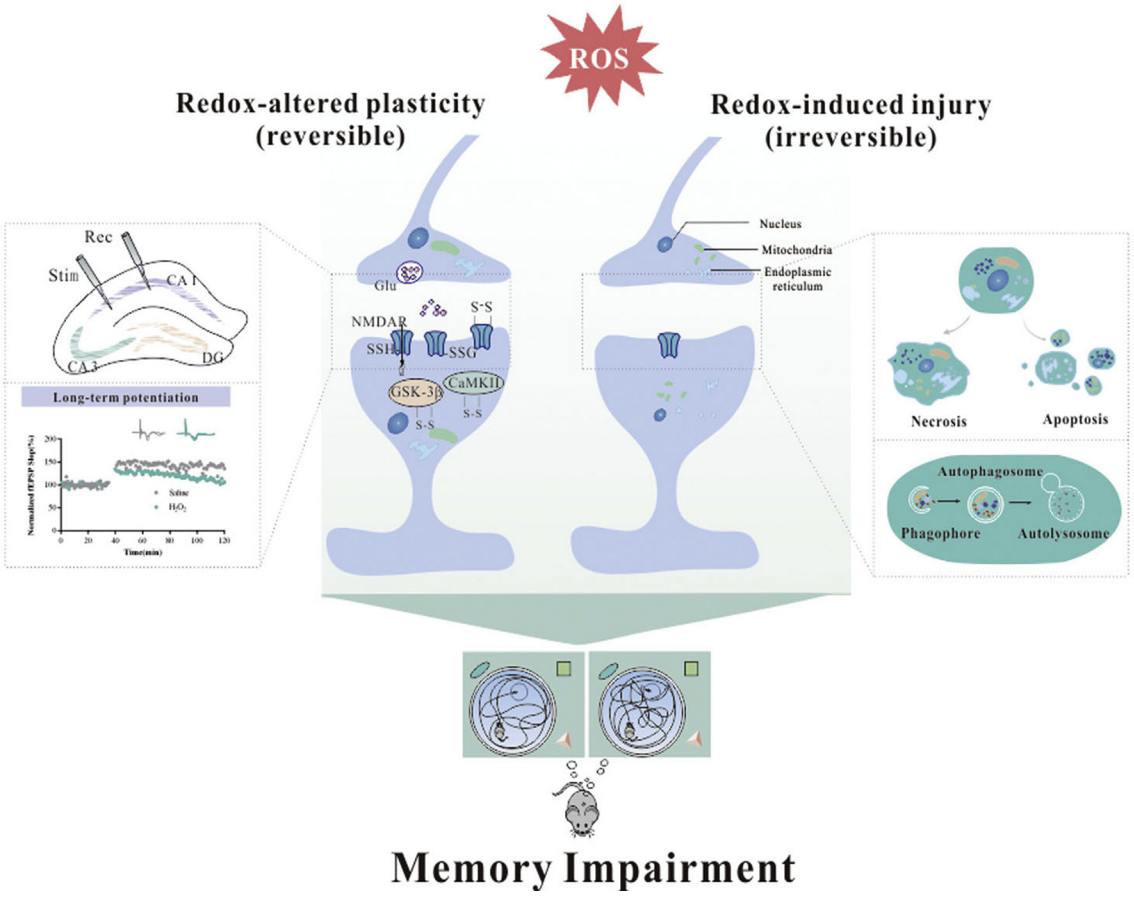


Figure 1 Two ROS-dependent mechanisms underlying cognitive disorders: redox-altered plasticity and redox-induced injury. Moderate ROS levels may reversibly affect synaptic plasticity *via* altering the function of molecular targets such as NMDAR, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and glycogen synthase kinase-3β (GSK-3β). In contrast, excessive amounts of ROS may cause irreversible neurotoxic effects to trigger neuronal apoptosis.

reported that the activation of GSK-3β underlies the inhibitory effect of Ch-T (20 μmol/L) on LTP in the hippocampus. To date, the key molecular mechanism underlying redox-altered plasticity remains unclear. Further investigations are required to specifically clarify the precise targets and their modification sites that underlie redox-altered plasticity.

4. Redox-altered plasticity and cognitive disorder

Oxidative stress contributes to the age-related impairment in cognitive functions[62]. In addition, dietary treatment with antioxidants such as vitamin E, vitamin C, and α-lipoic acid prevents the age-related impairment in LTP[63]. Many studies of animal models have suggested a pathological role for redox-altered plasticity in triggering cognitive disorders, including AD, VD, Down syndrome (DS) and AAMI.

Increased ROS production has been considered one of the primary events in AD pathogenesis[64]. As shown in the study by De Felice et al.[65], Aβ oligomers induce ROS generation through an NMDAR-dependent mechanism, and these changes are counteracted by memantine, an open channel NMDAR antagonist prescribed as a memory-preserving drug to patients with AD. Moreover, $A\beta_{1-42}$-induced impairments in hippocampal LTP are reversed by a mitochondria-targeted antioxidant, MitoQ, suggesting a causal relationship between mitochondrial ROS overproduction and Aβ-induced impairments in hippocampal synaptic plasticity[47]. Similar studies have reported a role for peroxiredoxin II (Prx II), a peroxidase that is involved in AD pathogenesis, in the LTP deficits underlying age-related oxidative damage[66]. Endophilin A1 (EP), a brain-specific protein that mediates ROS-induced signal transduction, contributes to the Aβ-induced synaptic injury and cognitive decline[67].

Based on accumulating pharmacological evidence, oxidative stress contributes to the cognitive impairment in patients with VD. Acupuncture, a form of treatment that involves inserting thin needles through a person's skin at specific points on the body, significantly improves the LTP and mitochondrial function of VD rats[68]. Liu et al.[69] reported a decrease in oxidative stress in the hippocampus and an amelioration of the cognitive impairment in VD rats treated with CZ-7, a new derivative of claulansine F, through NRF2-mediated antioxidant responses.

DS is one of the most common chromosomal disorders and is characterized by cognitive impairments and congenital heart defects. Increased ROS levels have been observed in individuals with DS[70]. According to Ko et al.[71], reducing reduction in ROS levels might be a beneficial treatment for DS. Ts65Dn (TS) mice are the most commonly used animal model of DS, because they exhibit various phenotypic characteristics of DS, such as cognitive deficits[72]. The cognitive impairments in the TS mice may be due to the altered synaptic plasticity and increased synaptic inhibition and oxidative damage. More specifically, TS mice showed a

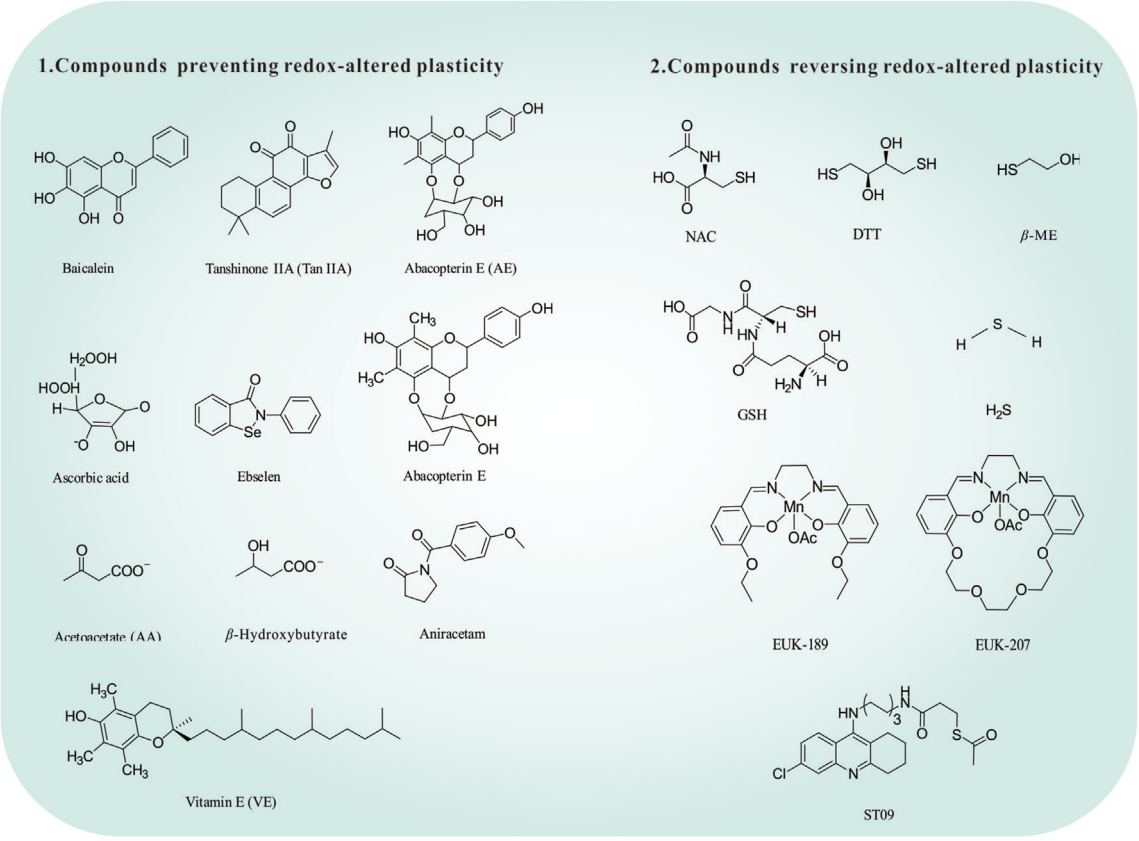


Figure 2 Chemical structures of compounds that prevent or reverse redox-altered plasticity.

remarkable reduction in LTP in the hippocampus[73]. As shown in the study by Corrales et al.[74], melatonin (0.5 mg/day) decreases the levels of lipid peroxidation and restores hippocampal LTP in TS mice, suggesting a relationship between LTP and ROS in TS mice.

Impairments in hippocampal LTP usually occur in aged animals, which is thought to be the basis of AAMI[7,75]. Previous studies have proposed a close association between AAMI and the ROS level[76]. In mammals, the age-related accumulation of oxidative damage has been observed in the brain[77], and an increase in antioxidant activity induced by chronic subcutaneous injections of two synthetic catalytic ROS scavengers, EUK-189 and EUK-207, almost completely reverses the cognitive deficits in the old animals[78]. Interestingly, the aging-related impairment in LTP is reversed by the acute administration of reductants that directly regulate thiol redox status, such as DTT or β-mercaptoethanol, but not by classical antioxidants, such as vitamin C or Trolox, although vitamin C also prevents redox-altered plasticity[75].

5. Targeting redox-altered plasticity to reactivate synaptic function

ROS are involved in the pathogenesis of many cognitive disorders. Most current antioxidant drugs are based on ROS-scavenging effects[26,79,80], thereby reducing the activation of subsequent stress responses and preventing redox-altered plasticity. Because the oxidation is not avoidable in daily activities and over-oxidation is generally harmful to the body, we should seriously consider whether we would rather use reductants to reverse the oxidation of key molecules to restore their function or use antioxidants to prevent the unavoidable oxidation occurring in daily activities. From this perspective, a reversal of redox-altered plasticity by erasing the accumulated oxidative damage, including key redox-modified plasticity-related proteins, is a more attractive choice to treat cognitive disorders. The application of compounds that regulate redox-altered plasticity may become a new intervention strategy for individuals with cognitive disorders. These compounds are divided into two types (Fig. 2): 1, compounds that prevent redox-altered plasticity and 2, compounds that reverse redox-altered plasticity.

5.1. *Compounds prevent redox-altered plasticity*

An increasing number of studies have highlighted the potential value of natural compounds extracted from fruits, vegetables and beverages as treatments for AAMI and neurological disorders[81]. Natural medicine ingredients from traditional medicinal herbs have shown to resist the oxidative stress-induced LTP impairment. For example, Wang et al.[35] did not observe an effect of tanshinone IIA on hippocampal LTP under physiological conditions, but it significantly prevented the impairment in LTP induced by H_2O_2. In addition, another natural flavonoid, abacopterin E, alleviates the LTP impairment induced by H_2O_2[82]. These effects are produced by the regulation of both ROS scavenging and signaling pathways. A combination of the ketone bodies acetoacetate (1 mmol/L) and β-hydroxybutyrate (1 mmol/L) prevents the H_2O_2 (200 μmol/L)-mediated impairment in LTP, and this neuroprotective effect of KB involves the inhibition of protein phosphatase 2A[83]. Lead is a pervasive neurotoxic metal that impairs synaptic plasticity and cognitive function through a redox-dependent mechanism. Karamian et al.[84] observed an amelioration of the Pb exposure-induced LTP impairment in rats treated with vitamin C *in vivo*.

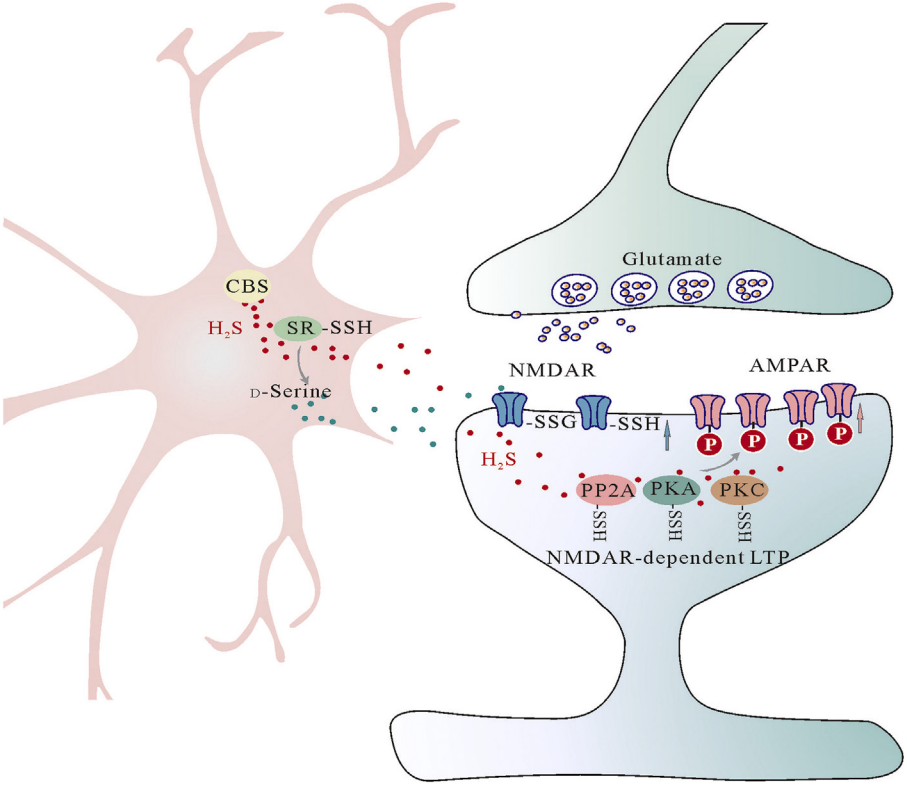


Figure 3 The mechanisms underlying H_2S-mediated regulation of NMDAR-dependent LTP and memory. H_2S is produced in astrocyte by cystathionine β-synthase (CBS) and then H_2S facilitates the induction of LTP *via* increasing D-serine availability, enhancing the activity of NMDA receptors and increasing the surface stability of AMPARs through an *S*-sulfhydration-dependent manner. SR, serine racemase; PP2A, protein phosphatase 2A; PKA, protein kinase A; PKC, protein kinase C.

Yang et al.[33] reported an effect of vitamin C on antagonizing the LTP impairment induced by H_2O_2. However, after oxidative stress exposure, vitamin C may not be able to restore redox-altered plasticity. In addition, vitamin E is an antioxidant that exerts protective effects on Pb intoxication. VE restores the Pb exposure-induced decreases in EPSP slopes[85]. The nootropic drug aniracetam is an analogue of piracetam, which is presumed to function as a memory enhancer, and it attenuates oxygen free radical-induced impairments in synaptic plasticity[86].

5.2. *Compounds reverse redox-altered plasticity*

Hydrogen sulfide (H_2S) is well-known for its toxicity and smell. Interestingly, H_2S has recently been shown to function as a third member of endogenous gasotransmitter family that mediates various physiological and pathophysiological functions[87,88]. The primary sources of endogenously produced H_2S in humans and other mammalians tissues are cystathionine β-synthase, mercaptopyruvate sulfurtransferase and cystathionine-γ lyase. Polysulfide (H_2S_n) mediates most of the biological functions of H_2S by sulfhydrating the $-$SH group of cysteine residue on targets, which is known as *S*-sulfhydration. A large number of proteins have been reported to be sulfhydrated by H_2S, including actin, GAPDH, nuclear factor κB, etc.[89]. The antioxidant actions of H_2S are well established in the cardiovascular system[90]. In the central nervous system, the neuroprotective effect and synaptic action of exogenous H_2S have attracted the interests of numerous researchers aiming to explore its therapeutic potential as a treatment for cognitive disorders[40]. Approximately twenty years ago, Battaglia et al.[8] reported that exogenous H_2S facilitates the induction of hippocampal LTP, a cellular model of memory, by increasing NMDAR activity. As shown in our recent study, the mechanisms underlying H_2S-mediated regulation of LTP include (Fig. 3): increasing D-serine availability[91], disinhibiting the zinc-mediated blockade of NMDAR[92] and increasing the surface stability of AMPARs[46] in a *S*-sulfhydration-dependent manner. Interestingly, H_2S rapidly reverses the LTP impairment in aged rats[91], indicating that the transfer of an oxidation status of receptors or other key regulators to a sulfhydration status may regenerate NMDAR activity. Our studies also revealed a requirement for the endogenous sulfhydration signal in LTP[91,92] and memory, indicating that supplementation with exogenous H_2S potentially represents a new therapeutic approach for the treatment of cognitive disorders. However, the precise mechanism underlying the regulatory effects of H_2S on memory still requires further investigation.

Sulfhydryl compounds such as DTT, 2-mercaptoethanol (β-ME), glutathione (GSH) and *N*-acetyl cysteine (NAC) are widely used in experiments or clinical therapy as redox agents. They display a broad range of biological functions that are mediated by multiple mechanisms, including the free radical-scavenging capacity[93], metal ion chelation[94] and modulation of post-translational modifications on cysteine residues[95–97]. In the central nervous system, sulfhydryl compounds also function as neuroprotective agents[98,99]. Disulfide bonds and/or sulfhydryl groups, which widely exist in most ligand-gated channel proteins and receptors to affect channel activity, have been shown to be involved in the direct upregulation of the activity of various types of receptors by sulfhydryl compounds, including NMDAR, GABAR and acid-sensing ion channels[95,100,101]. For instance,

NMDAR is modulated by reducing and oxidizing chemical agents[100,102,103]. Moreover, in recent decades, studies by our group and other labs revealed that mercaptan increases NMDAR-dependent LTP and reverses aging-related deficits in synaptic plasticity in the hippocampus[32,33,60,104]. These effects are closely associated with the redox effects of sulfhydryl compounds on NMDAR activity. Several studies have confirmed that mercaptans increase NMDAR activity through two mechanisms: a direct redox-dependent mechanism and an indirect mechanism depending on the activity of CaMKII[33,60,104,105].

Activity-dependent changes in synaptic strength, including LTP and LTD, are directly related to the trafficking of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) toward and away from the synapse in response to NMDAR activity[106−108]. Although the potentiating effect of mercaptans on NMDAR has been reported for thirty years, very little is known about whether these compounds affect AMPAR trafficking[109]. Recently, a posttranslational modification targeting the thiol group of cysteine residue, known as *S*-palmitoylation[110], was identified to be essential for the regulation of AMPAR surface trafficking[111−114]. *S*-Palmitoylation refers to the formation of a reversible thioester linkage between a palmitoyl lipid and the thiol group of a cysteine residue. Palmitoylation of $GluA_1$ and $GluA_2$ decreases their insertion into the plasma membrane[112−114]. From the chemical perspective, the formation of a thioester linkage on the cysteine residue might be disrupted by thiol reductants. Mercaptans also increased the surface stability of AMPARs *via* de-palmitoylation in our previous study[115].

The study by Wang et al.[104] from our group reported the development of novel multifunctional neuroprotective molecules by linking sulfhydryl groups to the structure of tacrine derivatives, and these sulfhydryl-containing molecules significantly enhanced NMDAR function. Liu et al.[116] reported a promising role for a novel thioester derivative of tacrine, ST09, in the treatment of VD. Thus, the introduction of a mercapto group into the structural skeleton of current nootropic drugs may represent a new research direction for drug development.

6. Summary and prospects

Two ROS-dependent mechanisms, including redox-altered plasticity and redox-induced injury, are involved in cognitive disorders. Redox-altered plasticity is more similar to functional changes rather than structural changes, and thus it may emerge as a window to provide interventions designed to alleviate memory impairments. Strategies targeting redox-altered plasticity using pharmacological agents might reverse synaptic dysfunctions in the early stage and alleviate memory abnormalities in individuals with cognitive disorders. Furthermore, the use of reductants to reverse the accumulated oxidative damage, rather than antioxidants to non-selectively prevent ROS generation during daily activities, may have greater therapeutic value. The application of compounds that reverse redox-altered plasticity may become a new intervention strategy for individuals with cognitive disorders.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No. 81773712 to Pengfei Wu, Nos. 81471377 and 81671438 to Fang Wang, Nos. 81473198 and 81673414 to Jianguo Chen) and Foundation for Innovative Research Groups of NSFC (No. 81721005 to Jianguo Chen and Fang Wang, China).

Author contributions

Pengfei Wu and Jianguo Chen conceived and designed the review. Pei Wang and Pengfei Wu retrieved the literature and drafted the manuscript. Pei Wang drew the Figures. Fang Wang and Jianguo Chen participated in the design of study and assessed the quality of study. Lan Ni, Fang Wang and Jianguo Chen revised the review.

Conflicts of interest

The author declares no conflicts of interest related to the content of this article.

References

1. Qiu J. Ticking time bomb faced by China's ageing population. *Lancet Neurol* 2007;**6**:582−3.
2. Bliss TV, Gardner-Medwin AR. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. *J Physiol* 1973;**232**:357−74.
3. Bliss TV, Collingridge GL. A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature* 1993;**361**:31−9.
4. Lynch MA. Long-term potentiation and memory. *Physiol Rev* 2004;**84**:87−136.
5. Kidd PM. Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment: Current understanding and progress toward integrative prevention. *Alternative Med Rev* 2008;**13**:85−115.
6. Rowan MJ, Klyubin I, Wang Q, Hu NW, Anwyl R. Synaptic memory mechanisms: Alzheimer's disease amyloid beta-peptide-induced dysfunction. *Biochem Soc Trans* 2007;**35**:1219−23.
7. Mothet JP, Rouaud E, Sinet PM, Potier B, Jouvenceau A, Dutar P, et al. A critical role for the glial-derived neuromodulator D-serine in the age-related deficits of cellular mechanisms of learning and memory. *Aging Cell* 2006;**5**:267−74.
8. Battaglia F, Wang HY, Ghilardi MF, Gashi E, Quartarone A, Friedman E, et al. Cortical plasticity in Alzheimer's disease in humans and rodents. *Biol Psychiatr* 2007;**62**:1405−12.
9. Foster TC. Regulation of synaptic plasticity in memory and memory decline with aging. *Prog Brain Res* 2002;**138**:283−303.
10. Tang LH, Aizenman E. Long-lasting modification of the *N*-methyl-D-aspartate receptor channel by a voltage-dependent sulfhydryl redox process. *Mol Pharmacol* 1993;**44**:473−8.
11. Lipton SA, Choi YB, Takahashi H, Zhang D, Li W, Godzik A, et al. Cysteine regulation of protein function-as exemplified by NMDA-receptor modulation. *Trends Neurosci* 2002;**25**:474−80.
12. Halliwell B. Reactive oxygen species and the central nervous system. *J Neurochem* 1992;**59**:1609−23.
13. Ibi M, Liu JJ, Arakawa N, Kitaoka S, Kawaji A, Matsuda K, et al. Depressive-like behaviors are regulated by NOX1/NADPH oxidase by redox modification of NMDA receptor 1. *J Neurosci* 2017;**37**:4200−12.
14. Jang EY, Ryu YH, Lee BH, Chang SC, Yeo MJ, Kim SH, et al. Involvement of reactive oxygen species in cocaine-taking behaviors in rats. *Addiction Biol* 2015;**20**:663−75.
15. Ravaglia G, Forti P, Maioli F, Bianchi G, Martelli M, Talerico T, et al. Plasma amino acid concentrations in patients with amnestic mild cognitive impairment or Alzheimer's disease. *Am J Clin Nutr* 2004;**80**:483−8.

16. Wang S, Irving G, Jiang L, Wang H, Li M, Wang X, et al. Oxidative stress mediated hippocampal neuron apoptosis participated in carbon disulfide-induced rats cognitive dysfunction. *Neurochem Res* 2017; **42**:583−94.
17. Ji MH, Qiu LL, Tang H, Ju LS, Sun XR, Zhang H, et al. Sepsis-induced selective parvalbumin interneuron phenotype loss and cognitive impairments may be mediated by NADPH oxidase 2 activation in mice. *J Neuroinflammation* 2015;**12**:182.
18. Rehman SU, Shah SA, Ali T, Chung JI, Kim MO. Anthocyanins reversed D-galactose-induced oxidative stress and neuroinflammation mediated cognitive impairment in adult rats. *Mol Neurobiol* 2017;**54**: 255−71.
19. Guo XD, Sun GL, Zhou TT, Wang YY, Xu X, Shi XF, et al. LX2343 alleviates cognitive impairments in AD model rats by inhibiting oxidative stress-induced neuronal apoptosis and tauopathy. *Acta Pharmacol Sin* 2017;**38**:1104−19.
20. Zheng Q, Zheng X, Zhang L, Luo H, Qian L, Fu X, et al. The neuron-specific protein TMEM59L mediates oxidative stress-induced cell death. *Mol Neurobiol* 2017;**54**:4189−200.
21. Gervais FG, Xu D, Robertson GS, Vaillancourt JP, Zhu Y, Huang J, et al. Involvement of caspases in proteolytic cleavage of Alzheimer's amyloid-beta precursor protein and amyloidogenic A beta peptide formation. *Cell* 1999;**97**:395−406.
22. Abramov AY, Scorziello A, Duchen MR. Three distinct mechanisms generate oxygen free radicals in neurons and contribute to cell death during anoxia and reoxygenation. *J Neurosci* 2007;**27**:1129−38.
23. Simon HU, Haj-Yehia A, Levi-Schaffer F. Role of reactive oxygen species (ROS) in apoptosis induction. *Apoptosis* 2000;**5**:415−8.
24. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 2007;**39**:44−84.
25. Niizuma K, Endo H, Chan PH. Oxidative stress and mitochondrial dysfunction as determinants of ischemic neuronal death and survival. *J Neurochem* 2009;**109**:133−8.
26. Qi S, Guo L, Yan S, Lee RJ, Yu S, Chen S. Hypocrellin A-based photodynamic action induces apoptosis in A549 cells through ROS-mediated mitochondrial signaling pathway. *Acta Pharm Sin B* 2019; **9**:279−93.
27. Colton CA, Colton JS, Gilbert DL. Changes in synaptic transmission produced by hydrogen peroxide. *J Free Radic Biol Med* 1986;**2**: 141−8.
28. Colton CA, Fagni L, Gilbert D. The action of hydrogen peroxide on paired pulse and long-term potentiation in the hippocampus. *Free Radical Bio Med* 1989;**7**:3−8.
29. Pellmar TC, Hollinden GE, Sarvey JM. Free radicals accelerate the decay of long-term potentiation in field CA1 of Guinea-pig hippocampus. *Neuroscience* 1991;**44**:353−9.
30. Avshalumov MV, Chen BT, Rice ME. Mechanisms underlying H_2O_2-mediated inhibition of synaptic transmission in rat hippocampal slices. *Brain Res* 2000;**882**:86−94.
31. Cai F, Wang F, Lin FK, Liu C, Ma LQ, Liu J, et al. Redox modulation of long-term potentiation in the hippocampus *via* regulation of the glycogen synthase kinase-3beta pathway. *Free Radical Bio Med* 2008;**45**:964−70.
32. Yang J, Hu ZL, Jiang B, Ni L, Jin Y, Chen JG, et al. Effect of chloramine-T on long-term potentiation at synapses between perforant path and dentate gyrus in hippocampus of rats *in vivo*. *Neurotoxicology* 2011;**32**:199−205.
33. Yang YJ, Wu PF, Long LH, Yu DF, Wu WN, Hu ZL, et al. Reversal of aging-associated hippocampal synaptic plasticity deficits by reductants *via* regulation of thiol redox and NMDA receptor function. *Aging Cell* 2010;**9**:709−21.
34. Wang W, Wang F, Yang YJ, Hu ZL, Long LH, Fu H, et al. The flavonoid baicalein promotes NMDA receptor-dependent long-term potentiation and enhances memory. *Br J Pharmacol* 2011;**162**: 1364−79.
35. Wang W, Zheng LL, Wang F, Hu ZL, Wu WN, Gu J, et al. Tanshinone IIA attenuates neuronal damage and the impairment of long-term potentiation induced by hydrogen peroxide. *J Ethnopharmacol* 2011;**134**:147−55.
36. Maalouf M, Rho JM. Oxidative impairment of hippocampal long-term potentiation involves activation of protein phosphatase 2A and is prevented by ketone bodies. *J Neurosci Res* 2008;**86**: 3322−30.
37. Bonett RM, Trujano-Alvarez AL, Williams MJ, Timpe EK. Biogeography and body size shuffling of aquatic salamander communities on a shifting refuge. *Proc Biol Sci* 2013;**280**:20130200.
38. Robillard JM, Gordon GR, Choi HB, Christie BR, MacVicar BA. Glutathione restores the mechanism of synaptic plasticity in aged mice to that of the adult. *PLoS One* 2011;**6**:e20676.
39. Droge W. Free radicals in the physiological control of cell function. *Physiol Rev* 2002;**82**:47−95.
40. Knapp LT, Klann E. Role of reactive oxygen species in hippocampal long-term potentiation: Contributory or inhibitory?. *J Neurosci Res* 2002;**70**:1−7.
41. Kamsler A, Segal M. Hydrogen peroxide modulation of synaptic plasticity. *J Neurosci* 2003;**23**:269−76.
42. Knapp LT, Klann E. Potentiation of hippocampal synaptic transmission by superoxide requires the oxidative activation of protein kinase C. *J Neurosci* 2002;**22**:674−83.
43. Huddleston AT, Tang W, Takeshima H, Hamilton SL, Klann E. Superoxide-induced potentiation in the hippocampus requires activation of ryanodine receptor type 3 and ERK. *J Neurophysiol* 2008;**99**: 1565−71.
44. Klann E. Cell-permeable scavengers of superoxide prevent long-term potentiation in hippocampal area CA1. *J Neurophysiol* 1998;**80**: 452−7.
45. Hu D, Serrano F, Oury TD, Klann E. Aging-dependent alterations in synaptic plasticity and memory in mice that overexpress extracellular superoxide dismutase. *J Neurosci* 2006;**26**:3933−41.
46. Kishida KT, Hoeffer CA, Hu D, Pao M, Holland SM, Klann E. Synaptic plasticity deficits and mild memory impairments in mouse models of chronic granulomatous disease. *Mol Cell Biol* 2006;**26**: 5908−20.
47. Ma T, Hoeffer CA, Wong H, Massaad CA, Zhou P, Iadecola C, et al. Amyloid beta-induced impairments in hippocampal synaptic plasticity are rescued by decreasing mitochondrial superoxide. *J Neurosci* 2011;**31**:5589−95.
48. Dumont M, Wille E, Stack C, Calingasan NY, Beal MF, Lin MT. Reduction of oxidative stress, amyloid deposition, and memory deficit by manganese superoxide dismutase overexpression in a transgenic mouse model of Alzheimer's disease. *Faseb J* 2009;**23**: 2459−66.
49. Potier B, Poindessous-Jazat F, Dutar P, Billard JM. NMDA receptor activation in the aged rat hippocampus. *Exp Gerontol* 2000;**35**: 1185−99.
50. Clayton DA, Grosshans DR, Browning MD. Aging and surface expression of hippocampal NMDA receptors. *J Biol Chem* 2002;**277**: 14367−9.
51. Barnes CA, Rao G, Shen J. Age-related decrease in the *N*-methyl-D-aspartate$_R$-mediated excitatory postsynaptic potential in hippocampal region CA1. *Neurobiol Aging* 1997;**18**:445−52.
52. Shankar S, Teyler TJ, Robbins N. Aging differentially alters forms of long-term potentiation in rat hippocampal area CA1. *J Neurophysiol* 1998;**79**:334−41.
53. Boric K, Munoz P, Gallagher M, Kirkwood A. Potential adaptive function for altered long-term potentiation mechanisms in aging hippocampus. *J Neurosci* 2008;**28**:8034−9.
54. Turpin FR, Potier B, Dulong JR, Sinet PM, Alliot J, Oliet SH, et al. Reduced serine racemase expression contributes to age-related deficits in hippocampal cognitive function. *Neurobiol Aging* 2011;**32**: 1495−504.

55. Omerovic A, Chen SJ, Leonard JP, Kelso SR. Subunit-specific redox modulation of NMDA receptors expressed in *Xenopus* oocytes. *J Recept Signal Transduct Res* 1995;**15**:811−27.
56. Kumar A, Foster TC. Linking redox regulation of NMDAR synaptic function to cognitive decline during aging. *J Neurosci* 2013;**33**: 15710−5.
57. Haxaire C, Turpin FR, Potier B, Kervern M, Sinet PM, Barbanel G, 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**:336−44.
58. Kohr G, Eckardt S, Luddens H, Monyer H, Seeburg PH. NMDA receptor channels: Subunit-specific potentiation by reducing agents. *Neuron* 1994;**12**:1031−40.
59. Silva AJ, Paylor R, Wehner JM, Tonegawa S. Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science* 1992;**257**:206−11.
60. Bodhinathan K, Kumar A, Foster TC. Intracellular redox state alters NMDA receptor response during aging through Ca^{2+}/calmodulin-dependent protein kinase II. *J Neurosci* 2010;**30**:1914−24.
61. Maiese K, Chong ZZ. Insights into oxidative stress and potential novel therapeutic targets for Alzheimer disease. *Restor Neurol Neurosci* 2004;**22**:87−104.
62. Giasson BI, Duda JE, Murray IV, Chen Q, Souza JM, Hurtig HI, et al. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. *Science* 2000;**290**: 985−9.
63. Murray CA, Lynch MA. Dietary supplementation with vitamin E reverses the age-related deficit in long term potentiation in dentate gyrus. *J Biol Chem* 1998;**273**:12161−8.
64. Butterfield DA, Lauderback CM. Lipid peroxidation and protein oxidation in Alzheimer's disease brain: Potential causes and consequences involving amyloid beta-peptide-associated free radical oxidative stress. *Free Radic Biol Med* 2002;**32**:1050−60.
65. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, et al. Abeta oligomers induce neuronal oxidative stress through an *N*-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J Biol Chem* 2007;**282**: 11590−601.
66. Kim SU, Jin MH, Kim YS, Lee SH, Cho YS, Cho KJ, et al. Peroxiredoxin II preserves cognitive function against age-linked hippocampal oxidative damage. *Neurobiol Aging* 2011;**32**:1054−68.
67. Yu Q, Wang Y, Du F, Yan S, Hu G, Origlia N, et al. Overexpression of endophilin A1 exacerbates synaptic alterations in a mouse model of Alzheimer's disease. *Nat Commun* 2018;**9**:2968.
68. Li H, Liu Y, Lin LT, Wang XR, Du SQ, Yan CQ, et al. Acupuncture reversed hippocampal mitochondrial dysfunction in vascular dementia rats. *Neurochem Int* 2016;**92**:35−42.
69. Liu DD, Yuan X, Chu SF, Chen C, Ren Q, Luo P, et al. CZ-7, a new derivative of claulansine F, ameliorates 2VO-induced vascular dementia in rats through a Nrf2-mediated antioxidant responses. *Acta Pharmacol Sin* 2019;**40**:425−40.
70. Komatsu T, Lee MCI, Miyagi A, Shoji H, Yoshino F, Maehata Y, et al. Reactive oxygen species generation in gingival fibroblasts of Down syndrome patients detected by electron spin resonance spectroscopy. *Redox Rep* 2006;**11**:71−7.
71. Ko JW, Lim SY, Chung KC, Lim JW, Kim H. Reactive oxygen species mediate IL-8 expression in Down syndrome candidate region-1-overexpressed cells. *Int J Biochem Cell Biol* 2014;**55**:164−70.
72. Rueda N, Florez J, Martinez-Cue C. Mouse models of down syndrome as a tool to unravel the causes of mental disabilities. *Neural Plast* 2012;**2012**:584071.
73. Costa AC, Grybko MJ. Deficits in hippocampal CA1 LTP induced by TBS but not HFS in the Ts65Dn mouse: A model of Down syndrome. *Neurosci Lett* 2005;**382**:317−22.
74. Corrales A, Vidal R, Garcia S, Vidal V, Martinez P, Garcia E, et al. Chronic melatonin treatment rescues electrophysiological and neuromorphological deficits in a mouse model of Down syndrome. *J Pineal Res* 2014;**56**:51−61.
75. Watson JB, Khorasani H, Persson A, Huang KP, Huang FL, O'Dell TJ. Age-related deficits in long-term potentiation are insensitive to hydrogen peroxide: Coincidence with enhanced autophosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II. *J Neurosci Res* 2002;**70**:298−308.
76. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. *Nature* 2010;**464**:529−35.
77. Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, et al. Gene regulation and DNA damage in the ageing human brain. *Nature* 2004;**429**: 883−91.
78. Liu R, Liu IY, Bi X, Thompson RF, Doctrow SR, Malfroy B, et al. Reversal of age-related learning deficits and brain oxidative stress in mice with superoxide dismutase/catalase mimetics. *Proc Natl Acad Sci U S A* 2003;**100**:8526−31.
79. Battogtokh G, Choi YS, Kang DS, Park SJ, Shim MS, Huh KM, et al. Mitochondria-targeting drug conjugates for cytotoxic, anti-oxidizing and sensing purposes: Current strategies and future perspectives. *Acta Pharm Sin B* 2018;**8**:862−80.
80. Wang J, Huang L, Cheng C, Li G, Xie J, Shen M, et al. Design, synthesis and biological evaluation of chalcone analogues with novel dual antioxidant mechanisms as potential anti-ischemic stroke agents. *Acta Pharm Sin B* 2019;**9**:335−50.
81. Liu Z, Wang W, Feng N, Wang L, Shi J, Wang X. Parishin C's prevention of Abeta 1−42-induced inhibition of long-term potentiation is related to NMDA receptors. *Acta Pharm Sin B* 2016;**6**: 189−97.
82. Lei Y, Fu W, Chen J, Xiong C, Wu G, Wei H, et al. Neuroprotective effects of abacopterin E from *Abacopteris penangian*a against oxidative stress-induced neurotoxicity. *J Ethnopharmacol* 2011;**134**: 275−80.
83. Maalouf M, Rho JM. Oxidative impairment of hippocampal long-term potentiation involves activation of protein phosphatase 2A and is prevented by ketone bodies. *J Neurosci Res* 2008;**86**:3322−30.
84. Karamian R, Komaki A, Salehi I, Tahmasebi L, Komaki H, Shahidi S, et al. Vitamin C reverses lead-induced deficits in hippocampal synaptic plasticity in rats. *Brain Res Bull* 2015;**116**:7−15.
85. Salehi I, Karamian R, Komaki A, Tahmasebi L, Taheri M, Nazari M, et al. Effects of vitamin E on lead-induced impairments in hippocampal synaptic plasticity. *Brain Res* 2015;**1629**:270−81.
86. Wang YF, Li CC, Cai JX. Aniracetam attenuates H_2O_2-induced deficiency of neuron viability, mitochondria potential and hippocampal long-term potentiation of mice *in vitro*. *Neurosci Bull* 2006; **22**:274−80.
87. Yan SK, Chang T, Wang H, Wu L, Wang R, Meng QH. Effects of hydrogen sulfide on homocysteine-induced oxidative stress in vascular smooth muscle cells. *Biochem Bioph Res Co* 2006;**351**: 485−91.
88. Chang T, Untereiner A, Liu J, Wu L. Interaction of methylglyoxal and hydrogen sulfide in rat vascular smooth muscle cells. *Antioxidants Redox Signal* 2010;**12**:1093−100.
89. Hourihan JM, Kenna JG, Hayes JD. The gasotransmitter hydrogen sulfide induces NRF2-target genes by inactivating the KEAP1 ubiquitin ligase substrate adaptor through formation of a disulfide bond between Cys-226 and Cys-613. *Antioxidants Redox Signal* 2013;**19**:465−81.
90. Liu YH, Lu M, Hu LF, Wong PT, Webb GD, Bian JS. Hydrogen sulfide in the mammalian cardiovascular system. *Antioxidants Redox Signal* 2012;**17**:141−85.
91. Li YL, Wu PF, Chen JG, Wang S, Han QQ, Li D, et al. Activity-dependent sulfhydration signal controls *N*-methyl-D-aspartate subtype glutamate receptor-dependent synaptic plasticity *via* increasing D-serine availability. *Antioxidants Redox Signal* 2017; **27**:398−414.
92. Luo H, Wu PF, Han QQ, Cao Y, Deng SL, Wang J, et al. Reactive sulfur species emerge as gliotransmitters to support memory *via* sulfuration-dependent gating of NR2A-containing *N*-methyl-D-aspartate subtype glutamate receptor function. *Antioxidants Redox Signal* 2019;**30**:1880−99.

93. Deneke SM. Thiol-based antioxidants. *Curr Top Cell Regul* 2000;**36**:151−80.
94. Kr zel A, Lesniak W, Jezowska-Bojczuk M, Mlynarz P, Brasun J, Kozlowski H, et al. Coordination of heavy metals by dithiothreitol, a commonly used thiol group protectant. *J Inorg Biochem* 2001;**84**:77−88.
95. Cho JH, Askwith CC. Potentiation of acid-sensing ion channels by sulfhydryl compounds. *Am J Physiol Cell Physiol* 2007;**292**:C2161−74.
96. Amato A, Connolly CN, Moss SJ, Smart TG. Modulation of neuronal and recombinant $GABA_A$ receptors by redox reagents. *J Physiol* 1999;**517**:35−50.
97. Ullian ME, Beck CN, Walker LP, Fitzgibbon WR, Morinelli TA. Thiol antioxidants regulate angiotensin II AT1 and arginine vasopressin V1 receptor functions differently in vascular smooth muscle cells. *Am J Hypertens* 2009;**22**:221−7.
98. Arakawa M, Ito Y. *N*-Acetylcysteine and neurodegenerative diseases: Basic and clinical pharmacology. *Cerebellum* 2007;**6**:308−14.
99. Pocernich CB, Butterfield DA. Elevation of glutathione as a therapeutic strategy in Alzheimer disease. *Biochim Biophys Acta* 2012;**1822**:625−30.
100. Aizenman E, Lipton SA, Loring RH. Selective modulation of NMDA responses by reduction and oxidation. *Neuron* 1989;**2**:1257−63.
101. Pan ZH, Bahring R, Grantyn R, Lipton SA. Differential modulation by sulfhydryl redox agents and glutathione of GABA- and glycine-evoked currents in rat retinal ganglion cells. *J Neurosci* 1995;**15**:1384−91.
102. Lipton SA, Choi YB, Pan ZH, Lei SZ, Chen HS, Sucher NJ, et al. A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds. *Nature* 1993;**364**:626−32.
103. Sucher NJ, Lipton SA. Redox modulatory site of the NMDA receptor-channel complex: Regulation by oxidized glutathione. *J Neurosci Res* 1991;**30**:582−91.
104. Wang Y, Guan XL, Wu PF, Wang CM, Cao H, Li L, et al. Multifunctional mercapto-tacrine derivatives for treatment of age-related neurodegenerative diseases. *J Med Chem* 2012;**55**:3588−92.
105. Herin GA, Du S, Aizenman E. The neuroprotective agent ebselen modifies NMDA receptor function *via* the redox modulatory site. *J Neurochem* 2001;**78**:1307−14.
106. Lei S, McBain CJ. Two Loci of expression for long-term depression at hippocampal mossy fiber-interneuron synapses. *J Neurosci* 2004;**24**:2112−21.
107. Yu SY, Wu DC, Liu L, Ge Y, Wang YT. Role of AMPA receptor trafficking in NMDA receptor-dependent synaptic plasticity in the rat lateral amygdala. *J Neurochem* 2008;**106**:889−99.
108. Citri A, Malenka RC. Synaptic plasticity: Multiple forms, functions, and mechanisms. *Neuropsychopharmacology* 2008;**33**:18−41.
109. Han J, Wu P, Wang F, Chen J. *S*-Palmitoylation regulates AMPA receptors trafficking and function: A novel insight into synaptic regulation and therapeutics. *Acta Pharm Sin B* 2015;**5**:1−7.
110. Guan X, Fierke CA. Understanding protein palmitoylation: Biological significance and enzymology. *Sci China Chem* 2011;**54**:1888−97.
111. Yang G, Xiong W, Kojic L, Cynader MS. Subunit-selective palmitoylation regulates the intracellular trafficking of AMPA receptor. *Eur J Neurosci* 2009;**30**:35−46.
112. Hayashi T, Rumbaugh G, Huganir RL. Differential regulation of AMPA receptor subunit trafficking by palmitoylation of two distinct sites. *Neuron* 2005;**47**:709−23.
113. Lin DT, Makino Y, Sharma K, Hayashi T, Neve R, Takamiya K, et al. Regulation of AMPA receptor extrasynaptic insertion by 4.1N, phosphorylation and palmitoylation. *Nat Neurosci* 2009;**12**:879−87.
114. Van Dolah DK, Mao LM, Shaffer C, Guo ML, Fibuch EE, Chu XP, et al. Reversible palmitoylation regulates surface stability of AMPA receptors in the nucleus accumbens in response to cocaine *in vivo*. *Biol Psychiatr* 2011;**69**:1035−42.
115. Han J, Zhang H, Wang S, Zhou J, Luo Y, Long LH, et al. Potentiation of surface stability of AMPA receptors by sulfhydryl compounds: A redox-independent effect by disrupting palmitoylation. *Neurochem Res* 2016;**41**:2890−903.
116. Liu JM, Wu PF, Rao J, Zhou J, Shen ZC, Luo H, et al. ST09, a novel thioester derivative of tacrine, alleviates cognitive deficits and enhances glucose metabolism in vascular dementia rats. *CNS Neurosci Ther* 2016;**22**:220−9.