Treatment Strategies of Age-Related Memory Dysfunction by Modulation of Neuronal Plasticity

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Abstract: One of the most remarkable features of the mammalian central nervous system is its ability to store large amounts of information for periods approaching a lifetime.

However, during the aging process cognitive domains, such as long-term (declarative) memory and working memory decline in some, but by far not all individuals. It is essential to understand the physiological changes that cause memory decline and also to elucidate why preserved memory abilities vary so greatly across individuals and memory tasks.

A generally accepted hypothesis has been that long-lasting activity-dependent changes in the efficacy of synaptic transmission in the mammalian brain are considered to be of fundamental importance for the storage of information. There is now a more detailed understanding of the changes in neuronal plasticity during aging at the molecular and systems levels. This review discusses recent findings on age-related changes in neuronal plasticity, which have opened up novel sites of action for therapeutic intervention.

Key Words: Synaptic plasticity, aging, learning, memory, long-term potentiation.

INTRODUCTION

Memory decline associated with normal aging, often referred to as AAMI (age-associated memory impairment), greatly reduces the quality of life and affects at least 50% of individuals in their 60s according to estimations. In response, increasing emphasis in recent years has been directed toward defining the neurobiological basis of age-dependent cognitive decline and toward developing therapeutic strategies to treat these deficits. Although by now multiple approaches are discussed, this review will give an update on the latest developments in this field.

One current hypothesis is that memories are formed and stored through processes requiring neuronal plasticity [for review see 1-6]. Plasticity refers to changes in the number, type and function of nervous system connections and in the morphology and function of glia and in neuron-glia interactions. Changes in the efficacy of synaptic transmission in the brain are believed to provide, at least in part, the cellular basis of learning and memory. In fact, learning and memory impairments have been attributed to a decrease in neuronal plasticity of the hippocampus complex [7,8]. Examples of such persistent modifications are long-term potentiation and long-term depression (LTP and LTD). Long-term potentiation can be defined as a long lasting increase in synaptic efficiency, which is induced by stimulation of afferent fibers. LTD is an enduring, activity-dependent decrease in synaptic strength induced by low-frequency stimulation, which results from a modest rise in intracellular postsynaptic Ca^{2+} [9]. Several studies describe deficits in LTP in aged (2 years) rodents [10-13]. Other work indicates that this does not hold across all conditions [14,15] and that the presence and magnitude of deficits depend on the stimulation patterns used to induce potentiation [16-18] and whether the animals were deficient in learning [19]. For example, LTP at 5 Hz in aged rats that did not show learning deficits was similar to that seen in young (4-6 months) controls [19].

Potentially important neuronal signalling systems for reversing age-related cognitive impairments will be addressed in this review and include the following: cholinergic systems, which are critical to the neural mechanisms mediating learning. Reduced nicotinic and muscarinic cholinergic neurotransmission are a hallmark of normal aging [20]. In addition, an increasing number of studies has demonstrated critical age-related changes in adenosinergic neurotransmission [21,22]. Adenosine concentration in many brain areas, such as the hippocampus and limbic cortex, is significantly increased in aging rats, in part by a more efficient formation of adenosine from ATP and by a decreased removal of extracellular adenosine [23,24]. Increasing evidence suggests that L-type voltage-sensitive calcium channel (L-VSCC) currents are elevated in CA1 neurons of the hippocampus in aged rats and rabbits [25,26]. Although the direct relationship between L-VSCC current increases and memory formation remains unclear, some data suggest that excessive Ca^{2+} influx through L-VSCCs may in fact be detrimental to memory formation. Neurotrophin signaling is a critical mechanism involved in synaptic plasticity, learning and memory and neuronal health [27,28]. During brain aging there is a fragile balance between neurotrophic factor support and dys-

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function. Strategies to maintain the balance toward support are a key goal of aging research. Two recent studies found that targeted inhibition of either a potassium channel-modifier subunit or a small conductance Ca^{2+} -activated K^+ channel can restore to aged mice, not only normal neuronal firing, but also normal learning and synaptic plasticity [29,30]. Examination of differences between young and old brains has revealed higher levels of reactive oxygen species (ROS) as well as increased levels of oxidative stress markers in aging animals as compared to young animals. Age-related LTP impairments in hippocampal area CA1 or the DG have been attributed in part to this increase in ROS levels [31].

In this review we discuss the contributions of potential pharmacological interventions to the field of synaptic plasticity, and also discuss the role of existing and putative drugs to reverse age-dependent deficits in learning and memory.

ACETYLCHOLINE

The cholinergic hypothesis, by which memory decline in human aging and dementia is linked to dysfunction of the cholinergic system in the brain, first emerged more than 20 years ago [20]. It arose from the finding that aging is accompanied by decreased acetylcholine (ACh) levels in the brain.

Two major classes of receptors for acetylcholine have been found in the CNS of vertebrates: the muscarinic type, mAChR, a seven transmembrane domain G protein-coupled receptor which is activated by muscarine (M1–M5 subtypes), and the nicotinic type, nAChR, a pentameric cation-gated receptors which is activated by nicotine (skeletal muscle and neuronal subtypes).

Normal aging is associated with a loss of subcortical cholinergic neurons [32,33]. In addition, reduced nicotinic cholinergic receptor (nAChR) density and affinity has been observed and, to a lesser extent, reduced muscarinic receptor density during aging [34,35].

Binding of acetylcholine to both of the muscarinic and the nicotinic receptors can change neuronal plasticity. The M1, M2 and M4 subtypes of muscarinic receptors are the predominant muscarinic receptors in the CNS. These receptors activate a multitude of signaling pathways important for modulating neuronal plasticity and feedback regulation of ACh release [36]. Muscarinic signaling has been shown to be involved in the induction of LTP [37,38]. Unfortunately, the lack of highly selective mAChR subtype receptor ligands has hampered progress in identifying the role of individual mAChRs as well as interactions between mAChR subtypes for a long time. Only recently these studies are greatly facilitated by the development of subtype specific toxins and mice lacking individual mAChR genes [39,40]. For example, the learning deficits of M2-deficient mice were associated with profound changes in neuronal plasticity studied in hippocampal slices [41].

The neuronal nicotinic receptors subtypes mainly present in the hippocampus are alpha7 and alpha4beta2. They are highly permeable to Ca^{2+}. The influx of Ca^{2+} through these nAChRs contributes to intracellular free Ca^{2+}, which, in turn, modulates neurotransmitter release and synaptic plasticity (long-term priming of neuronal networks to memory storage). It was shown that nAChR agonists facilitate the induction of hippocampal LTP [42,43].

Thus, theoretically there are multiple therapeutic interventions acting on neuronal plasticity conceivable that could reinstall the cholinergic balance in the aging brain and thereby overcome the age-dependent memory deficits. Most of the information on the feasibility of these approaches comes from animal models. Administration of mAChR agonists, such as oxotremorine, enhances inhibitory avoidance tasks in rodents [44,45]. Interestingly, a selective antagonist of presynaptically located muscarinic receptor 2, BIBN-99, also improved spatial memory performance in aged cognitively impaired rats [46]. Similarly, administration of nicotine or other nAChR agonists, such as GTS-21, enhances numerous forms of learning and memory, including aversive conditioning tasks [47-51] as well as spatial learning tasks [52-55]. Even in humans, the nAChR agonist nicotine increases attention and facilitates memory [56].

In addition to receptor targeting agents, acetylcholine precursors that enhance the availability of choline might also be used for therapeutic purposes. Common acetylcholine precursors are various forms of choline and lecithin [57].

In addition, acetylcholinesterase inhibitors might have promising therapeutic effects since expression of human acetylcholinesterase has been shown to induce progressive cognitive deterioration in mice [58]. AChE works by hydrolyzing ACh into choline and acetic acid at cholinergic synapses. Acetylcholinesterase is present in three isoforms: G1, which is present in the brain; G4, present in the brain and the neuromuscular endplate; and G2, present in skeletal muscle and bloodforming cells [59]. Blockers of this enzyme inhibit the degradation of the neurotransmitter in the brain and may in such a way overcome the reduced acetylcholine levels in the aged brain.

A number of acetylcholinesterase inhibitors such as tacrine, donepezil, physostigmine, metrifonate, rivastigmine and galantamine [60-64] were used in studies to investigate the memory-enhancing effect of acetylcholinesterase inhibitors. The three most commonly prescribed cholinesterase inhibitors are rivastigmine (Fig. (**1a**)), galantamine (Fig. (**1b**)) and donepezil (Fig. (**1c**)) [65]. Donezepil, 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-yl]-methylpiperidine hydrochloride, is marketed under the name Aricept and also known as E2020 [66]. Donepezil exists in both R and S isomers, and each is effective in treatment. Donepezil is a non-competitive inhibitor of AChE and therefore does not bind the active site. Binding occurs at the narrowest part of the channel leading to the active site. A dual mechanism of action has also been proposed for galantamine, which inhibits AChE and acts as an allosterically potentiating ligand on nicotinic ACh receptors. Galantamine can increase the probability of ACh-induced nicotinic channel opening, which could improve nicotinic cholinergic neurotransmission [67]. Both galantamine and donepezil are classified as short-acting or reversible agents since binding to acetylcholinesterase enzyme (AChE) is reversed within minutes. In contrast, rivastigmine is classified as an intermediate-acting or pseudo-irreversible agent due to its long inhibition of AChE of up to 10 hours [68]. Rivastigmine preferentially inhibits the G1

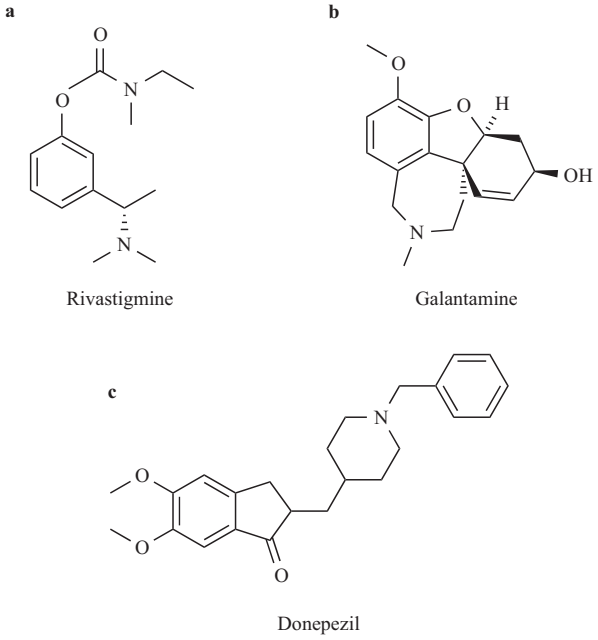


Fig. (1).

molecular form of AChE and is the only cholinesterase inhibitor to have exhibited preferential selectivity for any of the three isoforms of AChE [59].

There are a few disadvantages of the acetylcholinesterase inhibitors in treating cognitive impairments. First of all, many of the inhibitors cause peripheral cholinergic side effects. Secondly, cholinesterase-inhibitor therapy can compensate for the loss of ACh activity in presynaptic neurons only as long as the ACh receptors and postsynaptic neurons remain intact. Once the noncholinergic neurons in the brain also begin to degenerate, there is very little hope of slowing disease progression.

ADENOSINE

The adenosinergic system may also play an important role in cognitive deficits related to aging. Adenosine is an endogenous purine, which plays a crucial homeostatic function in the brain by coupling energy expenditure to energy supply and thereby controlling the metabolic rate in order to prevent energy depletion and subsequent cellular damage [69,70].

Adenosine has also evolved as an important molecule for both intracellular and extracellular signaling, functions that are distinct from its activity related to energy metabolism. This is particularly the case in the brain, which expresses high concentrations of adenosine receptors.

The adenosine receptor family contains four subtypes, A(1), A(2A), A(2B) and A(3), which all couple to G proteins and have the typical seven-transmembrane structure [71]. Originally it was reported that adenosine A(1) and A(3) interact primarily with Gi proteins and induce inhibition of adenylyl cyclase whereas adenosine A(2A) and A(2B) receptors couple preferentially to Gs proteins and thus stimulate adenylyl cyclase and increase cAMP levels [72-75]. Adenosine receptors, however, have also been reported to interact with other G proteins and to signal through various other pathways, independent of adenylyl cyclase, as reviewed recently [76]. The four different adenosine receptor subtypes have different affinities for adenosine. Whereas A(1) and A(2A) receptors have relatively high (nanomolar range) affinities for adenosine, A(2B) and A(3) receptors have a much lower affinity and are only activated at micromolar concentrations [69]. In many systems, basal extracellular adenosine concentrations are sufficient to tonically activate a substantial fraction of the high-affinity A(1) and A(2A) adenosine receptors. This review focusses on the role of these high affinity adenosine receptors in neuronal plasticity and age-related cognitive deficits.

Adenosine A(1) receptors are found throughout the brain, but show especially high expression in vulnerable areas like, for example, the hippocampus. Adenosine A(1) receptors are found both, pre- and postsynaptically in neurons, where they play an important role in inhibiting the release of excitatory neurotransmitters and inducing hyperpolarization, respectively. Adenosine acting mainly *via* the presynaptic A(1) receptor was shown to have an inhibitory action on LTP [77-80]. In contrast, the activation of A(2A) receptors results in a facilitation of neurotransmitter release [24]. These A(2A) receptors mostly act to fine-tune other neuromodulatory systems [23] and, among others, to control the tonic inhibitory action of A(1) receptors [81]. Thus, the control of neurotransmitter release by adenosine should be conceived as a balance between inhibitory A(1) and facilitatory A(2A) receptor-mediated actions [24].

The potential of adenosine to either inhibit or facilitate synaptic transmission makes this neuromodulatory system a likely candidate to be reset and to compensate the age-related changes in neuronal performance. In fact, previous studies have shown a decrease in the density of A(1) receptors and

an increase in the density of A(2A) receptors in the aged rats and mice [82-86]. This decrease in the density of A(1) receptors is accompanied by a decreased ability of A(1) receptor agonists to inhibit synaptic transmission in the hippocampus of aged rats [87] and an increased ability of A(2A) receptors to facilitate synaptic transmission in the hippocampus of aged rats. This facilitation is accompanied by a change in the main transduction system operated by hippocampal A(2A) receptors [22].

Whereas the stimulation of A(2A) receptor seems to have a compensatory action in older animals, activation of the A(1) receptor might still have a negative effect on neuronal plasticity. Recently, Rex and colleagues [21] showed a deficit in LTP already in middle-aged rodents, similar to that found in aged rodents [10-13]. This deficit could be eliminated by the A(1) receptor antagonist DPCPX (8-cyclopentyl-1,3-dipropylxanthine). In addition, adenosine produced greater depression of synaptic responses in slices from middle-aged versus young adult animals [21]. The authors hypothesize that the increased build-up of extracellular adenosine in older animals, which could be due to reduced adenosine clearance [24], activates the A(1) receptor-dependent LTP reversal effect [21] and might thus provide an explanation for memory losses during normal aging. In agreement with the modulatory role of adenosine in neuronal plasticity, agents regulating the action of adenosine receptors can affect learning and memory. Previous studies have demonstrated that adenosine receptor agonists (mainly A(1) agonists) disrupt learning and memory in rodents [88-90], while the non-selective blockade of adenosine receptors by theophylline or caffeine, as well as the selective blockade of A(1) and A(2A) receptors, facilitates rodent learning and memory in the passive avoidance task [91-93], the step-down inhibitory avoidance task [94] and the water maze task [95-97]. However, given at high doses, antagonists can produce an impairment [98], which might perhaps reflect a biphasic action of these agents. Furthermore, chronic administration of selective A(1) receptor agonists and antagonists may have effects on learning and memory, opposite to the effects elicited by acute administration of the same drugs [99,97]. Therefore, particular caution is required in development of adenosine-based strategies targeted at neurodegenerative or cognitive disorders in which chronic treatment is advocated. To date several pharmacological approaches to manipulate the adenosinergic system are available and can be divided in two categories: factors that indirectly increase the effectiveness of endogenous adenosine or substances that directly affect adenosine receptors.

Caffeine (1,3,7-trimethylxanthine or 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione), a member of a family of purine derivative methylated xanthines, has been suggested as a potential drug to counteract age-related cognitive decline. The central effects of caffeine are mainly mediated by its binding to adenosine receptors, principally A(1) and A(2A) receptors, in the brain [72]. Studies in rodents presented considerable evidence for cognition-enhancing properties of caffeine. However, clinical studies on the efficacy of caffeine to counteract or reverse age-related memory decline have been inconsistent, with some authors demonstrating an improvement of cognitive performance in aging individuals [100-102], with others showing no caffeine effects at all [103,104].

The synthetic purine derivative AIT-082 (Neotrofin, leteprinim potassium) is a *para*-aminobenzoic acid derivative of hypoxanthine, is currently under evaluation as a memory-enhancing agent in clinical trials investigating pharmacokinetics and tolerability [105,106]. AIT-082 has been shown to enhance cognition in both, mice [107,108] and rats [109]. AIT-082 improves both, long-term memory, as indicated by performance in a passive avoidance paradigm, and short-term memory, as indicated by performance in the win-shift paradigm [108]. In addition, AIT-082 has been shown to ameliorate age-induced memory impairment in mice [108] and memory deficits caused by ibotenic acid lesions of the basal forebrain in rats, as demonstrated in the Morris water maze [110]. The molecular basis for these actions of AIT-082 has not been fully elucidated but evidence for possible mechanisms is now accumulating. AIT-082 stimulates the synthesis and release of neurotrophic factors *in vitro* [110-112] and *in vivo* [113]. In addition, treatment of astrocyte cultures with AIT-082 causes an increase in the extracellular concentration of purines, such as adenosine [114]. It has recently been shown, that this is probably due to an inhibition of purine nucleotide phosphorylase and adenine deaminase [114]. From a pharmacological standpoint, it has been extremely difficult to develop potent drugs that interact with adenosine receptors. Adenosine-based drugs cause serious side effects because of the ubiquitous distribution of their receptors. A(1) receptor antagonists have, for example, shown undesirable psychomotor stimulant effects [115].

L-TYPE Ca^{2+} CHANNELS (L-VSCCs)

L-type voltage-sensitive calcium channels (L-VSCCs) are voltage sensitive channels that mediate long-lasting Ca^{2+} currents in response to depolarization in excitable cells. Brain L-VSCCs consist of five subunits: $\alpha 1$, $\alpha 2$, β, γ and δ [116, 117]. The $\alpha 1$ subunits form the ion-conducting pore of the channel and contain the binding sites for the dihydropyridine class of L-VSCC antagonists [118]. Several studies have shown that L-VSCC currents are elevated in CA1 neurons during aging [119-122]. It has been suggested that increased phosphorylation of L-VSCCs by cAMP-dependent protein kinase is responsible for the age-dependent up-regulation in neuronal L-VSCC activity [123]. Aged hippocampal neurons also show increased expression of $\alpha 1D$ [124], which are activated at significantly more hyperpolarized potentials than channels containing the $\alpha 1C$ subunit [125]. This may explain both, the robust L-VSCC-dependent potentiation [13] as well as the larger afterhyperpolarization (AHP) observed in hippocampal neurons from aged animals [25,26]. Increases in the AHP may contribute to impaired synaptic plasticity and memory decline in aged animals because the larger AHP impedes summation of incoming excitatory potentials in the aged neuron [8,126]. Based on these findings, it was speculated that selective L-VSCC antagonists might ameliorate age-dependent memory impairment. Antagonists of L-VSCCs are a heterogeneous group of drugs, which have been subdivided into three classes based on chemical structure, pharmacokinetics and therapeutic use: the dihydropyridines (DHP; e.g., nicardipine, nifedipine, nimodipine (Fig. (**2a**)), the benzothiazapines (e.g., diltiazem Fig. (**2b**)), and the phenylalky-

lamines (e.g., verapamil Fig. (**2c**)). Dihydropyridines can be chan-nel activators or inhibitors and therefore are thought to act allosterically to shift the channel toward the open or closed state, rather than by occluding the pore. Their receptor site includes amino acid residues in the S6 segments of domains III and IV and the S5 segment of domain III [127]. The dihydropyridine and phenylalkylamine receptor sites are close sharing some common amino acid residues. Phenylalkylamines are intracellular pore blockers, which are thought to enter the pore from the cytoplasmic side of the channel. Their receptor site is formed by amino acid residues in the S6 segments of domains III and IV, in close analogy to the local anesthetic receptor site of sodium channels [128-129]. Diltiazem and related benzothiazepines are thought to bind to a third receptor site, but the amino acid residues that are required for their binding overlap extensively with those required for phenylalkylamine binding. In brain slices from aged rats, nifedipine, a blocker of L-VSCCs, reverses the susceptibility to the induction of LTD using 1 Hz-stimulation and enhances the induction of NMDAR-dependent synaptic enhancement using 5 Hz-stimulation [130]. This finding might represent the electrophysiological basis for various reports on memory enhancing effects of L-VSCC blockers in aged animals. For example, nimodipine has been shown to improve passive avoidance retention in senescence-accelerated prone mice [131] trace eye-blink conditioning in aged rabbits [132-133], delayed matching to sample in senescent monkeys [134], and maze learning of aged rats [135,136]. Some of the described L-VSCC blockers are in clinical use already for other medical indications. Nimodipine (Nimotop®) was approved by the FDA for treating post aneurysm hemorrhage (bleeding). Nifedipine (Adalat® CC, Procardia XL®) is used for the treatment and prevention of angina pectoris resulting from coronary artery spasm as well as from exertion. Diltiazem is used to treat high blood pressure and to control chest pain. Verapamil has well documented efficacy for the treatment of tachycardial supraventricular arrhythmias (paroxysmal supraventricular tachycardia, atrial fibrillation with tachyarrhythmias, atrial flutter with rapid conduction). Allthough the amelioration in age-related memory decline in various animal models produced by L-VSCC antagonists makes them an attractive therapeutic tool to counteract memory loss associated with aging, one has to consider that L-VSCCs are also essential for the extinction of conditioned fear [137,138]. Thus, chronic blockade of L-VSCCs at concentrations necessary to treat certain memory deficits in elderly people could ultimately enhance other psychiatric disorders, such as anxiety disorders, because the same treatment would prevent the extinction of fear memories [139].

NEUROTROPHINS

Neurotrophins belong to a family of secretory proteins that include nerve growth factor (NGF), brain-derived neu-

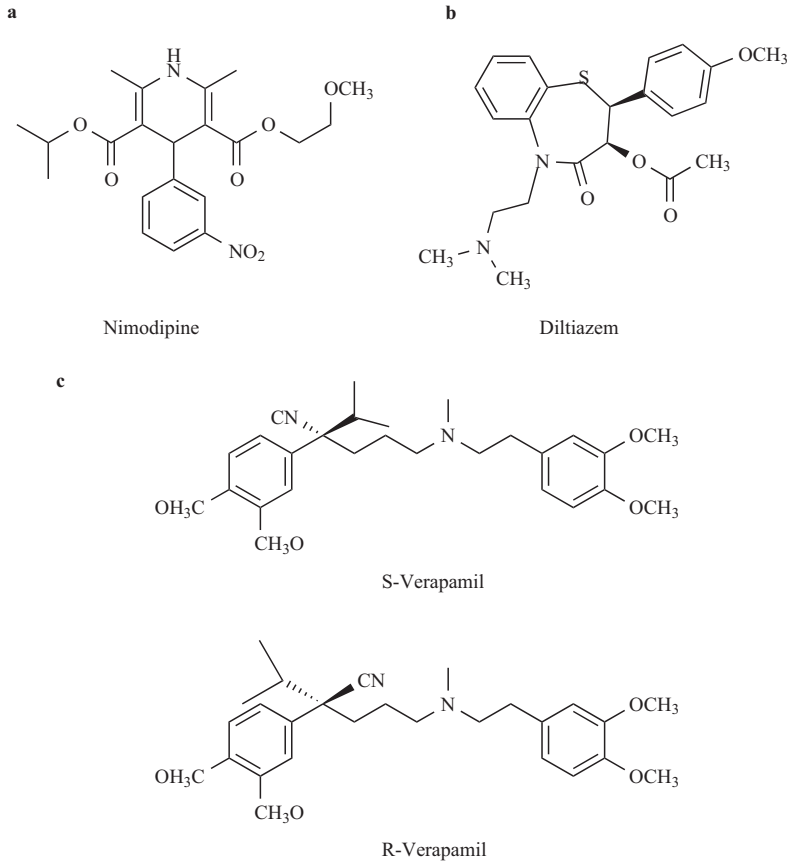


Fig. (2).

rotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5. These proteins initiate their biological functions by interacting with their cognate receptors. All neurotrophins bind to the p75 neurotrophin receptor (p75NR) [140], and each neurotrophin also binds to a specific Trk receptor tyrosine kinase: NGF binds to TrkA; BDNF and NT-4/5 to TrkB; and NT-3 to TrkC [141]. So far, all the synaptic functions of neurotrophins seem to be mediated by Trk receptors. In the mature nervous system, BDNF is involved in activity-dependent synaptic plasticity because BDNF expression increases in the hippocampus during learning-related events or after LTP-induction [27,142,143]. Intrahippocampal injection of BDNF has been demonstrated to improve specific spatial memory in rats [144]. The BDNF receptor TrkB modulates short-term synaptic function and LTP [145]. However, the role of BDNF in the aging brain is discussed in a controversial fashion. There is evidence that BDNF concentration is increased in DG homogenate obtained from aged rats [146]. In contrast there are studies, which show that BDNF (mRNA or peptide) levels do not seem to change dramatically during the aging process in rat hippocampus, suggesting that rather BDNF receptor alterations may occur with aging [28,147,148]. This hypothesis is supported by findings, which demonstrate that BDNF administration is not able to reverse spatial learning impairments in aged rats [149,150]. Interestingly, a clear association between hippocampal BDNF mRNA expression and memory performance of senescent rats is found in a study where non-impaired senescent rats show a higher post-training BDNF mRNA level in CA1 than the impaired animals [151]. In a very recent study, Monti *et al*. [152] found that BDNF is expressed at similar levels in the hippocampus of young-adult and aged rats, but the response to conditioned fear learning appears dysregulated by aging. Obviously further work will be required to clarify the role of BDNF during the aging process in the brain.

In the case of NGF the reported data are much more consistent. Using miniosmotic pumps, Bergado *et al*. [153] observed, that chronic intraventricular infusion with NGF in old cognitively-impaired rats ameliorates LTP deficits to levels equivalent to non-impaired rats. In line with this finding are reports, which describe that NGF infusion in aged rats ameliorates deficits in both spatial recent and reference memory, although the effects on spatial recent memory appear to be more robust [154-156]. A TrkA-selective NGF peptidomimetic termed D3 (580 Da), which binds at the IgC2 ectodomain of TrkA, was able to significantly improve learning and memory in cognitively impaired aged rats [157]. Besides the application of NGF as a purified protein, NGF administration to the basal forebrain of aged rats *via* grafts of either NGF-secreting fibroblasts or neural progenitor cells resulted in recovery of acquisition and retention of spatial learning of aged rats [158,159]. When basal forebrain neurons were transduced to produce NGF using the adeno-associated virus (AAV) vector system, an age-related decrease in the acquisition of the hidden platform in aged rats was prevented [160]. Similarly, intraseptal administration of mouse NGF with C-terminal myc-tag, using a recombinant adeno-associated virus serotype 2 (rAAV2) vector, reduced age-related deficits in spatial memory-related behavior in the Morris water task [161]. The reason for the effectiveness of NGF application in aged animals might be that the overall expression of TrkA mRNA in basal forebrain and caudate was found to be decreased in the impaired (-20%) as well as the severely impaired aged rats (-17%) [162].

Phosphatidylserine is a phospholipid that constitutes a major building block of the cell membrane. In humans with cognitive decline, it has been reported to improve scores for activity, social interactions, memory and learning [163]. Phosphatidylserine may help maintain levels of several neurotransmitters including NGF.

Increases in levels of NT-3 occurred in the murine hippocampus and cerebral cortex, respectively, during normal aging, but not during aging of mice with pathological changes [28]. Accordingly, aged rats showed improved acquisition and retention of spatial memory after a 4-week infusion period of NT-3, or NT-4/5 [149]. However, the impact of NT-3, or NT-4/5 on synaptic plasticity during aging is not clear at present. It can be speculated that ligand-independent signaling through TrkB receptors decreases glutamatergic synaptic strength during aging, if sufficient amounts of NT-3, or NT-4/5 are not available [164].

POTASSIUM CHANNELS (KVBETA1.1 AND SK)

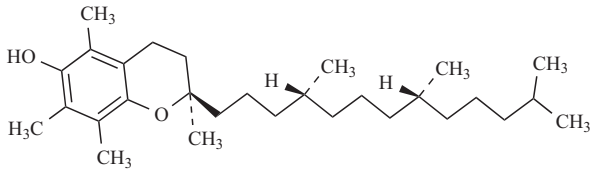
Voltage-activated potassium (Kv) channels are important determinants of membrane excitability that are involved in the regulation of wave forms and frequencies of action potentials and in the setting of thresholds and resting potentials of membranes. Kv channels from mammalian brain are hetero-oligomers containing alpha and beta subunits. Coexpression of Kv1alpha and Kvbeta1 subunits confers rapid A-type inactivation on noninactivating potassium channels (delayed rectifiers) in expression systems *in vitro*. Loss of function of Kv beta 1.1 subunits leads to a reduction of A-type Kv channel activity in hippocampal and striatal neurons [165]. Recently, Murphy *et al*. [29] reported that although slices from aged wild-type mice exhibited a modest level of potentiation 30–40 min after the tetanus, this potentiation was significantly less than the potentiation that resulted from the same tetanus in slices from aged Kvbeta1.1 knockout mice. In addition, they showed robust learning of the spatial reference memory task indicating that targeted deletion of the beta1.1 potassium channel subunit might reverse the process of cognitive aging. In the central nervous system, small conductance Ca^{2+}-activated K^+ (SK) channels are important for generating the afterhyperpolarizations seen after single or trains of action potentials [166-168]. Three SK channel subtypes (SK 1-3) are differentially distributed throughout the brain, but little is known about their specific expression in particular brain areas during aging. We have recently shown [30] that the expression of SK3 is highly elevated in the hippocampus of aged mice and contributes to reduced long-term potentiation (LTP) and impaired trace fear conditioning.

REACTIVE OXYGEN SPECIES (ROS)

ROS is a collective term that includes all reactive forms of oxygen, including both the radical and nonradical species that participate in the initiation and/or propagation of radical chain reactions. Ozone (O_3) is a toxic form of oxygen that oxidizes proteins, nucleic acids, and lipids. Singlet oxygen ($^1O_2$), which is largely involved in photochemical reactions, is reactive, although it does not contain unpaired electrons

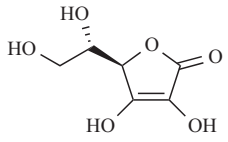
and therefore is not a free radical. It is formed *in vivo* by enzymatic activation of oxygen, for example, through lipo-oxygenase activity during prostaglandin biosynthesis [169]. Oxidative stress occurs when the generation of ROS in a system exceeds the system's ability to neutralize and eliminate them. The imbalance can result from a lack of antioxidant capacity caused by disturbance in production, distribution, or by an overabundance of ROS from an environmental or behavioral stressor. If not regulated properly, the excess ROS can damage a cell's lipids, protein or DNA, inhibiting normal function. Therefore, oxidative stress has been implicated in a growing list of human diseases as well as in the aging process [170-172]. Oxidative stress may lead to damage to molecules such as DNA, lipids, or proteins. Meccocci *et al*. [173] reported that aging causes damage to mitochondrial DNA in human brain and that the amount of damage to mitochondrial DNA (mtDNA) was 10-fold higher than that of nuclear DNA. There is strong evidence that mitochondrial dysfunction results in neurodegeneration [173]. The brain is particularly vulnerable to oxidative stress because it consumes large amounts of oxygen, has abundant lipid content, and a relative paucity of antioxidant levels compared to other organs [174]. Examination of differences between young and old brains has revealed higher levels of ROS as well as increased levels of oxidative stress markers in aging animals as compared to young animals [175-177]. Increases in ROS would then cause lipid peroxidation affecting the biophysical properties of membranes (i.e. decreases AA and thus increases membrane rigidity). Resulting deficits in LTP [31] could also be observed in hippocampal slices from young animals after application of hydrogen peroxide [178,179]. There is convincing evidence that dietary supplementation with the antioxidant Vitamin E (Fig. (**3a**)), Vitamin C (Fig. (**3b**)), α-lipoic acid (Fig. (**3c**)) or omega-3 fatty acids (Fig. (**3d**)) reverses the age-related decrease in α-tocopherol concentration and restores the ability to sustain LTP in aged rats [180-182]. The data suggest that age-dependent LTP deficits are triggered by increased lipid peroxidation, which in turn is triggered by interleukin-1β (IL-1β), most likely through formation of reactive oxygen species [183]. It was further observed that if membrane arachidonic acid concentration in hippocampus of aged rats is restored to levels observed in young rats reversed by dietary supplementation with arachidonic acid and its precursor γ-linolenic acid, the impairment in LTP is reversed [184]. Several studies have indicated that also behavioral deficits of aged animals are associated with increases in oxidative stress [185-187]. Typically, aged animals were fed with a diet high in antioxidants to test the hypothesis that cognitive function could be restored or even preserved with the help of antioxidants. Supplements (straw-

a



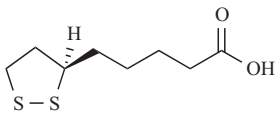
Vitamin E

b



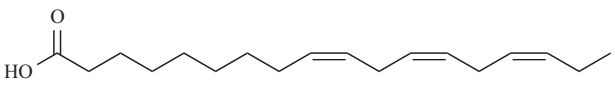
Vitamin C

c



α-Lipoic Acid

d



Linolenic Acid

Fig. (3).

berry, spinach, or blueberry at 14.8, 9.1, or 18.6 g of dried aqueous extract per kilogram of diet, respectively) fed for 8 weeks to 19-month-old Fischer 344 rats were effective in reversing age-related deficits in Morris water maze performance [188]. Rats, which were fed the potent free radical scavenger alpha-lipoic acid exhibited improved spatial learning and memory [189,190]. Chronic systemic administration of two synthetic catalytic scavengers of reactive oxygen species, Eukarion-189 (EUK-189) and EUK-207, almost completely reversed deficits in fear conditioning. Further, this treatment fully prevented increase in protein oxidation and decreased the increase in lipid peroxidation by ≈50% [191]. Altogether these findings suggest that reductions in the rate of ROS generation during aging by antioxidants will minimize protein oxidation and facilitate intracellular repair mechanisms to maintain synaptic plasticity and cognitive function.

CONCLUSIONS

Current research on the mechanisms of memory is opening an exciting era of experimental therapeutics. Characterization of synaptic plasticity changes during aging is contributing to our understanding of its effects on age-dependent memory decline. The effects of various different compounds, each with different chemical structures, on synaptic plasticity and memory indicate potentially fruitful therapeutic approaches to reverse age-related memory decrement, and give rise to the assumption that new classes of targets may soon emerge.

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