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Review Article

Roles of sigma-1 receptors in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of senile dementia all over the world. Still no existing drugs can effectively reverse the cognitive impairment. However, Sigma-1 (σ-1) receptors have been long implicated in multiple neurological and psychiatric conditions over these years. In this review, we discuss the current understanding of σ-1 receptor functions. Through regulation of lipid rafts, secretases, kinases, neuroceptors and ion channels, σ-1 receptors can influence cellular signal transduction, TCA cycle, oxidative stress, neuron plasticity and neurotransmitter release etc. Based on this, we suggest the key cellular mechanisms linking σ-1 receptor to Alzheimer's disease. Besides, we detail the evidences showing that σ-1 receptors agonists, being the promising compounds for treatment of cognitive dysfunction, exhibit robust neuroprotection and anti-amnesia effect against Aβ neurotoxicity in the progress of Alzheimer's disease. The evidence comes from animal models, preclinical studies in humans and full clinical trials. In addition, the questions to be solved regarding this receptor are also presented. When concerned with NMDAR, σ-1 receptor activation may result in two totally different influences on AD. Utilization of σ-1 agents early in AD remains an overlooked therapeutic opportunity. This article may pave the way for further studies about sigma-1 receptor on Alzheimer's disease.

Keywords: Sigma-1 receptor, Alzheimer's disease, pathogenesis, Aβ neurotoxicity, NMDA receptor

Introduction

Characterized by progressive cognitive dysfunction and behavioral impairment, Alzheimer's disease (AD) is a neurodegenerative disorder with insidious onset. So far the most widely accepted pathology of AD comprises amyloid-β deposition and neurofibrillary tangles of hyperphosphorylated tau protein. But no existing drugs can effectively reverse the cognitive impairment. Recently, σ-1 receptor has shown an emerging new look of improving cognitive function, especially its anti-amnesic and neuroprotective effects [1]. An early postmortem study reported that σ-1 receptor were decreased in hippocampus CA1 region of AD patients [2]. Later M. Mishina found σ-1 receptor loss in the early phase of AD using Positron emission tomography (PET) with (11C) SA4503. The binding potential was significantly decreased by 44-60% in the frontal, temporal, and occipital lobe, cerebellum and thalamus [3]. Based on changes of σ-1 receptor density, the following research over these years observed that σ-1 receptor agonists can significantly reduce AD induced cognitive dysfunction. Thus, we aim at highlighting the prospect of sigma-1 receptor effects and treatment in the progress of Alzheimer's disease.

Characteristics and biological effects of σ receptor

Sigma (σ) receptor was first identified as subtype of opioid receptor [4]. It independently established a receptor family after Quirion R proposing its difference from opioid receptor and phencyclidine binding site [5]. σ receptors can be divided into 2 subtypes: σ-1 and σ-2. Still there are disputes over the existence of σ-3 subtype. σ receptors are abundant in the body, especially in the central nervous system. It has high density distribution in the spinal cord, pons, medulla oblongata, red nucleus, cerebellum, hippocampus , medium density distribution in the cerebral cortex and hypothalamus and low density distribution in the basal ganglia and thalamus [6]. Study comparing σ1 versus

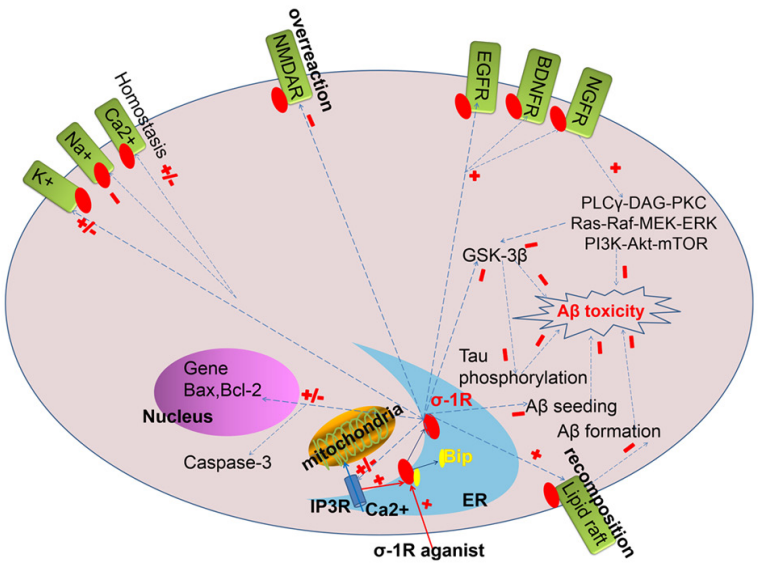

Figure 1. The possible mechanism of σ-1 receptor in the profession of Alzheimer's Disease.

σ2 receptor found their dramatic difference in size, distribution and ligand affinity [7]. To date, σ-1 receptor has been cloned g in guinea-pig and human [8, 9] and, then, in rat and mouse [10, 11]. Its gene encodes a protein of 223 amino acid with two transmembrane domains and a typical endoplasmic reticulum localized signal near the short N terminus [12]. But so far there is no mammalian protein can specifically bind to this receptor. σ-2 receptor has not yet been cloned and little knowledge is known about its relationship with AD. Recently, Izzol et al. found that Aβ1-42 exhibits synaptic toxicity after binding to the σ-2/PGRMC1 receptor [13]. However, it is generally believed that σ-1 receptor plays a more important role in the progression of Alzheimer's disease.

In normal times, σ-1 receptors mainly localize on the mitochondrial associated endoplasmic reticulum membrane (MAM), forming a Bip chaperone structure with high sensitivity to the calcium ion. When activated by agonists such as cocaine or analgesic, σ-1 receptors separate from BiP and translocate from MAM to other parts of the cell. Through regulation of inositol triphosphate (IP3) receptors, N-methyl-D-aspartic acid receptor (NMDA) receptors, dopamine (DA) receptors and ion channels, σ-1 receptors can influence TCA cycle, oxidative stress [14], mitochondrial function, neuron plasticity and neurotransmitter release such as 5-hydroxy tryptamine, glutamate, dopamine, norepinephrine, acetylcholine, γ-aminobutyric acid and so on [15].

Potential mechanisms of σ-1 receptor in the progression of Alzheimer's disease

Despite of the mounting evidence on the etiology and pathogenesis of AD over these decades, the exact cause has not been fully elucidated, which may be attributed to the complexity and multiple factors related to it. Here, we suggest the key cellular mechanisms linking σ-1 receptor to Alzheimer's disease (**Figure 1**).

Aβ cascade hypothesis

Considered as multi-gene inherited disease with genetic heterogeneity, AD can be generally divided into familial AD and sporadic AD. Now three different autosomal dominant gene have been found to be related to early-onset AD: presenilin-1 (PS-1), presenilin-2 (PS-2) and amyloid precursor protein (APP). However, only one predisposing gene for late-onset AD is universally recognized, namely APOE epsilon 4 (APOEε4). Recently, emerging technologies to analyze the entire genome in large data sets have revealed new genes associated with late-onset AD risk, including ABCA7, BIN1, CASS4, CD33, CD2AP, HLA-DRB5-DBR1and so on [16]. Unfortunately, to date there is no evidence that combines AD related genes to σ-1 receptors. Only a few researches on correlation between risk for developing AD and σ-1 receptor gene mutation polymorphism have been reported. Some typical studies are discussed in subsequent sections of this paper. Among the 4 discovered AD genes, mutation of APP, PS-1 and PS-2 has been found to increase Aβ generation while APOEε4 results in Aβ deposition. Substantial evidence suggests the imbalance of amyloid beta production and clearance is the initial event in neuronal degeneration and dementia, which is also the common pathway of other cause in the pathogenesis leading to AD.

Different mechanisms could be evoked to describe the nature of σ-1 receptor alleviating

Aβ neurotoxicity: (i) σ-1 receptors may have effective protection against Aβ toxicity by modulating recomposition of lipid rafts, inhibiting Aβ fibrin formation [17]. Substantial amounts of the aspartyl protease β-secretase (BACE-1) and γ-secretase [18] localize in lipid rafts, where Aβ production occurs preferentially. What's more, GM1 ganglioside-bound amyloid β protein (GM1/Aβ), a seed proposed to be involved in initiation of amyloid fibril formation, is also associated within lipid rafts on the plasma membrane [19, 20]. Chronic activation of σ-1 receptor results in its translocation from the endoplasmic reticulum (ER), within lipid droplets, towards the lipid rafts on cytomembrane where it may involve in recomposition of lipid rafts and modifying cellular functions including signal transduction of protein coupled receptor, biosynthetic or endocytic traffic of protein [21]. Therefore, sustained σ-1 receptor activation may preferentially translocate to lipid rafts, on which binding sites are actively involved in Aβ production and transportation.

(ii) Attenuate Aβ25-35-induced Aβ1-42 seeding in hippocampal neurons [22]. Administration of Aβ25-35 can provoke a significant increase in APP expression and activation of the β-secretase pathway resulting in the endogenous Aβ peptide content in hippocampus, which is called Aβ seeding [23]. σ-1 receptors can block this process by regulation the Akt and glycogen synthase kinase-3β (GSK-3β) activity [22].

(iii) Facilitate cognition protection against Aβ through NMDAR response in various brain areas such as hippocampus and prefrontal cortex [24-26]. Pharmacology inhibition of NMDA receptor function, either by systemic administration of compounds directly into the brain or by crossing the blood brain barrier, results in impaired spatial learning and passive avoidance learning [27, 28]. σ receptors can potentiate pyramidal neurons in CA3 [29] region of dorsal hippocampus to NMDA (excitatory activation) and NMDA-dependent CA1 synapses [30], which is indispensable for learning ability and spatial memory storage. Besides, σ-1 receptors can prevent Aβ-associated NMDAR neurotoxicity [31].

(iv) Potentiate ATP/IP3-induced Ca^{2+} influx on endoplasmic reticulum and plasma membranes, thus protecting the cognitive performance of rodents impaired by Aβ neurotoxicity or antagonists of voltage-dependent calcium channels in various learning tests [1]. σ-1 receptors not only localize in endoplasmatic reticulum, but also in nuclear and plasma membranes and on mitochondria [32-36], on which binding sites are involved in the regulation of calcium mobilization. Furthermore, σ-1 receptor protects mitochondria and neural viability by maintaining intracellular calcium homeostasis.

(v) Overexpression of σ-1 receptors potentiate lipid rafts-associated NGF, EGF and BDNF effect [1] and NGF-induced neuroprotection through regulating PLCγ-DAG-PKC, Ras-Raf-MEK-ERK and PI3K-Akt-mTOR signaling pathways [37]; Since the discovery of growth factor receptors localizing in lipid rafts [21], sustained activation of σ-1 receptors may be beneficial for cell survival rate and, therefore, facilitate neuroprotection or neuronal recovery against Aβ neurotoxicity. In addition, σ-1 receptors can enhance the axonal and dendritic growth in hippocampus [38].

(vi) Mitigate Aβ25-35-induced apoptosis by decreasing expression of proapoptotic gene Bax and the death protease caspase-3 whereas preserving antiapoptotic gene Bcl-2 levels, resulting in a concomitant enhancement in cell survival.

Tau protein hypothesis

Widely expressed in the nervous system, tau protein is a microtubule-associated protein, to catalyze microtubule assembly and stabilize microtubule structure. Being a defining pathological characteristic of AD, tauopathies may consists of increased resistance to proteolytic enzymes and the subsequent formation of hyperphosphorylation tau, paired helical filaments (PHF-tau), neurofibrillary tangles (NFTs) deposits and, consequently, neuron death. Glycogen synthase kinase-3 (GSK-3) has been shown to be the key kinase that mediates tau hyperphosphorylation [22]. However, the molecular process underlying over activation of GSK-3 and its potential linkage to AD pathologies in vivo remain unclear. σ-1 receptor could prevent alterations in GSK-3β activity: (i) block the reduction of P(Ser473)-Akt/Akt ratio; (ii) phosphorylate Ser9 residue of GSK-3β by enhancing PI3K/Akt and PLCγ/PKC signaling pathway [39] suppressed in Aβ incubation.

Thus, Tau hyperphosphorylation and neurofibrillary tangles could be alleviated to maintain the neuronal cytoskeleton stability.

Neurotransmitter hypothesis

Modulation of acetylcholine release: Cholinergic neurotransmitter is a principal process underlying the cognitive function, especially for memory storage. The cholinergic neurons in basal forebrain, nucleus basalis, cerebral cortex, amygdaloid complex and hippocampus were observed to be indispensable for learning and memory formation [40, 41]. In normal aging, some cortical cholinergic activity can be slightly lost whereas patients suffering from AD or related dementias present a severe decline in acetylcholine levels, which can be attributed to a corresponding reduction in choline acetyltransferase (chAT) and acetylcholinesterase (AchE) [42-44].

Both in vitro and in vivo, σ-1 receptors are potent modulators of acetylcholine release. These proteins can upregulate the KCl-evoked or electrically evoked release of ^{3}H-acetylcholine from rat frontal cortex and hippocampus [45-48]. In the meanwhile, acetylcholine release in the striatum was marginally affected [49-51]. Therefore, σ-1 receptors, with less undesired side effects seen in AChE inhibitors [50], alleviate the Aβ-induced dysfunction of cholinergic that are implicated in AD [52].

Modulation of glutamate release: Besides the well-known deficits of cholinergic activity, the neurotransmitter glutamate can also be reduced in AD. Both neurotransmitters are supposed to play key roles in memory [53, 54]. σ-1 receptor represents a strategy for modulating glutamatergic levels: (i) Brain-derived neurotrophic factor (BDNF) associated glutamate release are potentiated by not only pharmacological activation but also overexpression of σ-1 receptor. It seems to occur via the involvement of PLCγ/IP3 pathway [55]. (ii) Elevation of the intracellular Ca^{2+} levels, which is released from the endoplasmatic reticulum, plays a vital role in spontaneous glutamate release [56, 57]. (iii) The effect also appears to be mediated via alpha-1 adrenergic and dopamine receptor [57, 58].

Thus, regulation of glutamate levels by σ-1 receptor in the frontal cortex and hippocampus could be an additional mechanism underlying the anti-amnesic action.

Inflammation hypothesis

Since McGeer et al. [59] put forward that AD probably results from the inappropriate activation of immune and inflammatory response, a window of opportunity appears for introductions of disease-modifying regimens in AD. The inflammation pathology may arise from the extracellular Aβ deposits and become later enhanced by aggregates of tau. Driven by activated microglia [60], astrocytes and inflammatory factors, the overactive response increases as the disease progresses and, finally, results in the "wrong direction" to attack the normal nervous tissue, causing synapses damage and neurons death.

Abundantly expressed in immunocyte of central immune system, σ-1 receptor activation can not only maintain pro-inflammatory and anti-inflammatory homeostasis [61], but also preserve the neuronal viability [62]. The possible mechanism is as follows: (i) reduce activation and damage of microglial from Aβ25-35-evoked apoptosis; Microglial is the only immune cell type present in the organotypic hippocampal slice. By blocking intracellular calcium signals, many aspects of microglial activations such as cytoskeleton rearrangement, migration, and cytokines production were suppressed. In addition, the activators like lipopolysaccharide (LPS), monocyte chemoattractant protein 1 (MCP-1) and adenosine triphosphate (ATP) can loss the enhancing effect on microglia [63]. (ii) Prevent T-cell mediated immunity by potentiating the anti-inflammatory cytokine IL-10 [64]; (iii) the neuroprotective effects against inflammation at delayed time points maybe mutually adjusted by central and peripheral immune system [65].

In short, lack of σ receptors, neurocyte will be more vulnerable to Aβ-mediated amyloid toxicity. The intracellular lipid metabolism, cell skeleton network and immune response will be more easily damaged, thus accelerating the neural degeneration and oxidative stress-caused neural death, which contribute greatly to the etiology of AD.

Research on σ-1 receptor and Aβ neurotoxicity

The hallmark changes of AD comprise Aβ deposition and neurofibrillary tangles due to tau protein hyperphosphorylation. Aβ neurotoxicity comes both from the aggregation state and soluble oligomeric β. With the ability to stimu-

lating hyperphosphorylation of tau protein, the extracellular Aβ aggregation is considered to be the main molecular mechanisms of AD. However, it is still unclear how Aβ acting on the σ receptors expression. At present, studies on σ receptor with AD are limited to receptor ligands, mainly including endogenous and exogenous ligand.

Endogenous ligand

Neurosteroids might be the endogenous ligands for σ receptors such as dehydroepiandrosterone and luteal hormone [66]. With insufficient level and lower affinity for σ receptors, the title of endogenous ligands has been controversial [67]. Pregnenolone (PREG) and dehydroepiandrosterone (DHEA), being σ-1 receptor ligands under physiological conditions, can improve the memory and learning ability in a cholinergic and NMDAR-dependent way [56]. It has been early demonstrated that levels of PREG in the hippocampus is strongly correlated to the memory performance of rodents or aged rats [52]. For instance, post-training injection of PREGS into the hippocampus and amygdala of mice enhances the recollection for foot shock active avoidance training [68]. On the other hand, administration of DHEA could also ameliorate memory deficits induced by Aβ25-35. In particular, DHEA improves the axonal, dendritic growth [38] or even neural stem cell survival rate [69].

Although the exact mechanisms in positive cognitive effects by neurosteroids are not fully understood, it is suggest that the endogenous agents regulates a series of ion channels such as γ-aminobutyric acid-type A($GABA_A$) receptors [70], N-methyl-daspartate (NMDA) receptors [71] and voltage-gated Ca^{2+} channels [72]. Meyer DA [56] found that PREGS selectively leads to a robust increase in the frequency of mEPSCs and glutamate release from presynaptic terminals, which may rely on an elevation in intracellular Ca^{2+} levels triggered by activation of presynaptic $G_{i/o}$ protein coupled σ-1 like receptors. Moreover, PREG has been recently shown to rescue the reduction of PI3K/Akt and Ras/ERK signals in Aβ25-35-mice [31] while DHEA activates σ-1 receptors, enhancing the growth of neuronal projections through a modulation of PI3K-Akt-mTOR-p70S6k signaling in Aβ25-35-impaired newborn neurons [37].

Exogenous ligand

Exogenous σ-1 receptor agonists show potential anti-amnesia and neuroprotection effect on both pharmacological and pathological models. Marrazzo, A first proved σ-1 receptor agonist PRE-084 and MR-22 (-), without involvement of NMDA receptors blockade, can reduce Aβ-mediated cortical neurons toxicity [73] to slow down the progression of Alzheimer's disease. They projected the σ-1 proteins may obstruct the neurodegenerative process other than excitotoxic death. Based on this, Donepezil, licensed for symptomatic treatment of mild to moderate AD, was found to attenuate Aβ and glutamate toxicity [74] and potentiate the axonal growth [1] with its cholinergic and σ-1 agonistic properties. Additionally, afobazole mitigate neuron apoptosis through modulation of gene Bax, Bcl-2 expression and death protease caspase-3 levels in response to Aβ. Furthermore, treatment with afobazole decreased microglial activation and prevented disruption of ATP signaling in microglia incubated in Aβ25-35, indicating its potent preservation of microglial function after Aβ exposure. Last but not least, afobazole maintains intracellular proinflammatory and anti-inflammatory homeostasis [61] and potentiate NGF-induced neurite outgrowth [75]. Recently, it is clearly proposed that ANAVEX2-73, a mixed σ-1/muscarinic receptor ligand, can efficiently decrease the hyper-activation of GSK-3β in AD and prevent both the Tau hyperphosphorylation and Aβ1-42 Seeding [22]. Still there are (+) pentazocine and SA4503 alleviating amyloid load in pharmacology of a biphasic bell-shaped dose response curve. The protective effects of σ-1 receptors mentioned above can be mostly blocked by σR antagonists such as haloperidol and BMY-14802.

As for roles of exogenous ligand in cognitive improvement, with vivo microdialysis in freely moving rats, (+)-SKF10,047 was demonstrated to increase extracellular acetylcholine in both frontal cortex and hippocampus in a stereoselective way, which could also be blocked by haloperidol [48, 76]. Besides, σ-1 agonists have shown anti-amnesic efficacy in both pharmacological and pathological models, which include cholinergic destruction, Aβ administration, normal aging, senescence accelerated mouse (SAM), glutamatergic/serotonergic or calcium channel deficits [1]. Intriguingly, in most behavioral tests, σ-1 receptor ligands do

not facilitate or impede the learning ability in the control groups, suggesting that it is under pathological conditions that σ-1 receptors are activated [1].

Overall, σ-1 receptor agonists, being the promising compounds for the treatment of cognitive dysfunction, exhibit robust neuroprotection and anti-amnesic effect against Aβ neurotoxicity.

Research on σ-1 receptor and psychotic symptoms

In addition to the character of acquired impairment in cognitive function, AD exert a gradual bad impact on the patient's professional social and family activities. The earliest non-cognitive expressions such as various types of depressive and anxiety disorder may develop [77] whereas behavioral disorders, aggression, hallucinations occur in late AD. There is still no effective clinical drug against these psychiatric symptoms. The role of σ receptors, especially σ-1 subtype, has been long identified as a target for pathophysiology in neuropsychiatric disorders. However, the preclinical and clinical evidence of σ-1 receptor on AD psychotic symptoms is meager at present.

Behavioral models have suggested some ligands that bind to σ receptors possess "antidepressant and anxiolytic" like properties [78]. Urani A [79] demonstrated that when AD rats were submitted to the conditioned fear stress test, igmesine and (+)-SKF-10,047 can significantly reduce the stress-induced motor suppression, indicating exogenous σ-1 receptor agonists may alleviate AD-associated depressive symptoms. Besides, BMY-14802, a σ-1 antagonist with potential antipsychotic activity, shows its potential anxiolytic properties by reducing dorsal raphe and hippocampal release of 5-HT in a direct interaction with somatodendritic 5-HT (1A) receptors in the raphe nuclei [80]. On the other hand, synergistic stimulation of σ and 5-HT (1A) receptors is requested in acute antidepressant-like action of OPC-14523 [81].

Early clinical trials of some antipsychotic drugs have exhibited a certain affinity for σ-1 proteins [82]. For example, haloperidol [83], a σ-1 receptor antagonist, have better effect on controlling the agitation, hostility and aggression. Panamesine (EMD 57445) [84], with high affinity for σ-1 receptor, has antipsychotic effects and is free of side effects related to the extrapyramidal motoric system (EPMS). What's more, memantine (10 μM) [85], licensed for use in moderate to severe AD [86], had been demonstrated to improve the bradykinin induced mobilization of intracellular Ca^{2+} in NG108-15 neuroblastoma cells, mimicking effect of σ-1 against PRE-084 (1 μM). Still there are many antipsychotics like Chlorpromazine and Nemonapride with high affinity for σ-1 proteins.

Thus, σ-1 receptor ligands may presents a promising effect either as individual or adjuvant on the accompanying psychotic symptoms in AD. However, large double-blind randomized placebo-controlled clinical trials are needed to confirm its treatment prospect.

Clinical research and application of σ-1 receptor in Alzheimer's disease

Research on correlation between risk for developing AD and σ-1 receptor gene mutation polymorphism is not much. The first study, a Japanese case-control sample [87], showed TT-P haplotype a protective factor for AD. The subsequent Polish study, however, did not validate the findings [88]. Recently, A. Feher [89] found TT-P gene mutation of σ-1 receptor to be the risk factors against AD. With no consistency, these observations suggest that a clinical study with larger sample size and greater ethnic similarity is necessary.

Fluvoxamine, as a selective serotonin reuptake inhibitor (SSRI) and σ-1 receptor against, is considered by Izzo, N.J to be an alternative approach in alleviating delirium [90] in patients with Alzheimer's disease. However, there are no clinical evidence showing fluvoxamine has any therapeutic effect in cognitive disturbance of patients with AD though some case reports exist in Depression and Schizophrenia [91, 92]. In contrast to other SSRIs including sertraline and paroxetine, it has been suggested that Fluvoxamine, as a potent sigma-1 receptor agonist, may reduce Aβ-mediated neurotoxicity through increasing phosphorylation of Akt-1 [93]. To date, only a few σ-1 receptor agonists (SA4503 and ANAVEX2-73) [22, 94, 95] have entered phase II clinical trials of acute/chronic neurodegenerative disorders.

Therefore, despite the increasing positive experimental results, utilization of σ-1 agents

early in the disease process remains an overlooked therapeutic opportunity.

Dispute over σ-1 receptor role in Alzheimer's disease

Recently, Tackenberg et al. holds that Aβ induces Tau-dependent neurodegeneration and dendritic spine loss via pathway involving NR2B/NR2A-containing NMDAR [96], considering NMDAR to be closely linked with the progression of AD. Soon after this, Sha et al. proved that NMDAR action is downregulated through reducing NR2B phosphorylation in σ-1 receptors knockout mice [97]. Therefore, it is projected that the σ-1 receptors deficits in AD brain, by decreasing NR2B phosphorylation, can reduce the Aβ-enhanced Ca^{2+} influx across NMDAR and prevent NMDAR-mediated neurotoxicity, which is proved by Yin, J. lately. Yin, J. et al. provides, for the first time, in vivo evidence that σ-1 receptor deficiency can attenuate Aβ25-35-induced hippocampal neuronal death and spatial cognitive deficits. Either σ-1 receptor deficiency or the blockade of σ-1 receptor in this study can significantly reduce the Aβ25-35-induced neuronal death. Paradoxically, there have been enormous reports describing the neuroprotection of σ-1 agonists in Aβ25-35/1-42 mice [98-100]. Although PREGS had also been observed to amplify NMDA-induced excitotoxicity in cultured hippocampal neurons [101], the discrepancy is hard to be reconciled. Exact timing of σ-1 receptors activation was raised to explain the contradictory effects. Administration of σ-1 receptor antagonists within 48 h post-Aβ25-35 can block the Aβ-neurotoxicity through suppressing NMDAR. However, after 72 h of Aβ25-35-injection, neuronal injury can be mitigated by σ-1 activation through enhancing ERK/PI3K-Akt signaling cascade [31] or decreasing levels of oxidative stress [102]. They also proposed that downregulation of PKC and reorganization of lipid rafts by σ-1 receptor deficiency can suppress NR2B subunit-containing NMDAR [103].

However, evidence in adverse effect of σ-1 receptor on AD is insufficient. Besides, NMDAR-mediated responses, traditionally been regarded as a double-edged sword, controversially interacted with σ-1 receptors over these decades. For example, σ ligands, including haloperidol, (+)-pentazocine, (+)-SKF-10,047 and DTG, depress NMDAR currents in Xenopus oocytes [104]. In addition, Kume et al. provided that σ-1 receptor ligands with affinity for NMDAR may act as neuron protector through reducing Ca^{2+} influx through NMDAR [105]. However, neurosteroids PREG as σ-1 agonist, have two-ways regulation of NMDAR function. Yang found σ-1 receptor activation by PREGS can suppress NMDAR response to resist neurocyte death in Aβ25-35-mice [31] Whereas Chen et al. suggested PREGS lead to NR2B tyrosine phosphorylation and Ca^{2+} influx through NMDAR, which cascaded the ERK/CREB pathway crucial for NMDAR-dependent long-term potentiation (LTP) involving in synaptic plasticity [106]. Contrarily to the results above, a large number of evidences consider the σ-1 receptor to be an accelerator for NMDAR response. It has been early demonstrated that σ-1 receptor can reverse OBX (olfactory bulbectomy)-induced NMDA-impaired behaviors [107]. Moreover, σ receptors facilitate pyramidal neurons in CA3 region of dorsal hippocampus to NMDA (excitatory activation) [29] and potentiate NMDA-dependent CA1 synapses [30], which is indispensable for learning ability and spatial memory storage. Nonsteroid hormones like progesterone and testosterone act as antagonists of σ-1 and, consequently, of NMDA-mediated responses [1]. Generally, σ-1 receptor exerts dual-directional regulation on NMDAR function. Nevertheless, the mechanism how σ-1 receptors act on NMDAR-mediated responses has not yet been explained. Martina supposed that σ-1 modulates NMDAR synaptic transmission and plasticity via blocking the small conductance Ca^{2+}-activated K^+ current (SK channels) in rat hippocampus [108]. On the other hand, it is possibly attributed to the additional diversity of NMDAR responses arising from the complexity of subunit composition and variations in localization. Synaptic NMDAR, with numbers of subunits NR2A>NR2B [109], can activate the nuclear calcium signaling pathways to promote the synaptic plasticity and improve the neural excitatory. Instead, activation of extrasynaptic NMDAR, with numbers of subunits NR2A<NR2B, causes calcium overload in neurons and starts the apoptosis or death pathway [110, 111]. Therefore, as far as the NMDAR itself, the imbalance between the two different pathways can cause pathogenesis in neural degenerative diseases, especially for AD.

Thus, we propose that when concerned with NMDAR, σ-1 receptor activation may result in

two totally different influences on AD: (a) facilitation of cognition improvement through modulating NMDAR-dependent learning and memory; (b) aggravation of the Aβ-mediated neurotoxicity by NR2B subunit-containing NMDAR in apoptosis or death pathway. Further studies are urgently needed to evaluate the exact process of its dual effect on both AD and NMDAR subtypes response.

Conclusion

An increasing studies show that σ receptor is implicated in cellular differentiation, neuroprotection, neuroplasticity and anti-amnesia of the brain, which suggests its potential prospects in the treatment of cognitive deficits. But several questions regarding this receptor are still open. There is no σ receptor ligands applied in current clinic. Only a few σ-1 agonists have entered phase II clinical trials of neurodegenerative disorders. Results of correlation studies between AD and variation of σ receptor gene polymorphism are not yet unified. When it comes to the NMDAR response, further studies are needed to evaluate whether σ receptors aggravate the NMDAR-dependent neural apoptosis. What's more, cause of lower density of σ-1 receptors in early phase of AD is still unknown. With little knowledge of how Aβ acting on the σ receptors expression, the existing research on σ receptor is limited to endogenous and exogenous ligands. Besides, specific endogenous ligands have not been deeply studied. However, either as individual or adjuvant agent, σ receptor ligand is bound to be beneficial for degenerative disease of CNS, especially for AD-related cognitive impairment, and may provide an alternative to AchEIs/memantine which is currently available. The mechanism of how Aβ acting on the σ receptors expression is becoming a new direction for pathogenesis of AD.

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Disclosure of conflict of interest

None.

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