From Synaptic Dysfunction to Memory Recovery: Ampakine Compounds as Potential Therapeutic Agents for Alzheimer's Disease

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Abstract

Alzheimer's disease, a profoundly impactful neurodegenerative condition, manifests as the progressive deterioration of memory and cognitive functions. Studies have shown that memory decline is associated with a decrease in the rapid transmission of excitatory signals between neurons. The limited research on the positive impact of AMPA receptor modulation has prompted the exploration of Ampakine compounds. Ampakines enhance long-term potentiation (LTP) by activating receptors, which exists in a crucial role in memory preservation. The ability of ampakine compounds to bind to AMPA receptors and increase the expression of neurotrophic factors, such as BDNF, is believed to mitigate LTP impairment. Recent studies have demonstrated that certain ampakine compounds can enhance consciousness and memory storage by promoting the production of various neurotrophins, particularly BDNF and NGF. Previous research has shown that neurotrophins contribute to synaptogenesis, the formation of new connections between neurons, primarily

through dendritic spines. Increasing synaptogenesis via dendritic spines positively impacts signal transmission and retention by strengthening neuronal connections. This review highlights the potential of ampakine compounds such as pesampator and hydroflumetazide to enhance synaptic interactions, alleviate symptoms of Alzheimer's disease, and specifically address memory loss through their effects on neurotrophins.

Keywords: Alzheimer’s disease, AMPA receptors, Ampakine, Neurotrophins, Synaptogenesis

Introduction

L-Glutamic acid, a fundamental neurotransmitter, possesses dual roles as both a neuromodulatory switch and a regulator of synaptic function and neural pathways. The glutamate system holds immense importance in maintaining the apppropriate performing of the mammalian central nervous system and takes place a significant position in the development of various neurodegenerative diseases. This system exhibits diverse functions through two distinct receptor families: ionotropic glutamate receptors and metabotropic glutamate receptors. Ionotropic glutamate receptors function as ligand-gated ion channels, generating excitatory currents upon binding with glutamate compounds. Metabotropic glutamate receptors are G protein-coupled receptors that initiate intracellular cascades via G protein-mediated signaling events. Within the glutamate system, ionotropic receptors are further classified into three subfamilies known as AMPA, NMDA, and kainic acid receptors based on the specific agonists that bind to them. Despite sharing some structural similarities, ionotropic glutamate receptors are categorized based on differences in their structures, functions, and pharmacological characteristics (Golubeva et al, 2023; Evans,2021; Partin,2015; Lauterborn et al, 2016; Lee et al, 2016).

AMPA receptors are completely distributed all of the the central nervous system and facilitate rapid signal transmission. Their crucial involvement in synaptic plasticity, a mechanism essential for enhancing memory, positions them as an ideal target for developing drug classes suitable for treating conditions for instance Alzheimer's, epilepsy, and Parkinson's disease. Given these factors, there is significant interest among academic institutions and pharmaceutical companies worldwide in exploring various ligands that interact with AMPA receptors and conducting studies to understand their properties (Golubeva et al, 2023; Reiner, 2018; Brogi et al, 2019; Hansen et al, 2021; Evans et al, 2021; Partin, 2015; Lauterborn et al, 2016; Lee et al, 2016).

Alzheimer's disease is fundamentally qualified by a gradual loss of memory, decline in cognitive features, and disturbances in behavior. The diagnosis of this debilitating disease is often confirmed through postmortem examinations. It is estimated that approximately 10% of individuals aged 65 or older and a staggering 47% of those aged 85 or older are affected by this condition (Traynelis et al, 2010). Consequently, a significant

proportion of the elderly population requiring long-term care is diagnosed with dementia, with approximately 25 to 30% of cases specifically classified as Alzheimer's disease. Common behavioral manifestations among Alzheimer's patients encompass symptoms such as agitation, sleep disturbances, aggression, inappropriate sexual behavior, and depression (Traynelis et al, 2010).

This review highlights the significant correlation between ampakines and the processes involved in memory formation and storage in the human brain. Neurotrophic factors, which can't penetrate the blood–brain barrier, may potentially be expressed in various parts of the brain, particularly the hippocampus and cerebral cortex. Thus, the stimulation of neurotrophic factors through ampakine compounds could prove beneficial. The utilization of ampakine compounds has enough power to stimulate the expression of neurotrophins in the brain, leading to notable morphological changes in synapses concurrent with the effects of neurotrophins. Consequently, strengthening memory storage and other factors associated with memory through the use of ampakines could be considered a promising therapeutic approach in the cure of Alzheimer's disease.

1. Positive Regulators of AMPA-Type Glutamate Receptors

Ampakines are one class of drug compounds that exert allosteric effects on ionotropic glutamate receptors. These compounds effectively delay the deactivation and desensitization of AMPA receptors.

Ampakines own the potential to enhance the stimulation of long-term potentiation (LTP), which is associated with improved human memory storage. Ampakines can also reverse deficits in LTP, suggesting their involvement in the mechanisms of synaptic plasticity. As positive modulators of AMPA receptors, ampakines play a significant role in facilitating synaptic plasticity (Lynch, 1998). AMPA receptors are crucial receptors involved in the rapid spread of excitatory signals in the brain. Ampakines are a class of positive allosteric modulators that target AMPA glutamate receptors (Lynch, 1998). By increasing the duration and strength of AMPA receptor currents, which enhance neuronal size through NMDA receptor-mediated calcium influx, the induction of long-term potentiation (LTP) is magnified. Since LTP is considered a substrate for various forms of

learning, enhancing the function of AMPA receptors also improves memory. This understanding guided to the improvement of a novel class of drugs known as AMPAKINES (Lynch, 1998). Ampakines enhance AMPA receptor currents and readily cross the blood–brain barrier, effectively enhancing *in vivo* LTP induction. They act as positive regulators and do not exhibit detectable agonist/antagonist effects, instead modulating AMPA receptors after neurotransmitter binding (Lynch,1998).. Advancements in understanding LTP formation have provided important clues for developing drugs aimed at enhancing cognitive function. Notably, LTP induction involves unblocking voltage-dependent NMDA receptor channels and increasing postsynaptic calcium levels. However, two factors deviate from this understanding: 1) AMPA receptor-mediated short currents that sustain depolarization and 2) cortical telencephalic neurons that receive robust feed-forward GABAergic connections, which help balance and modify excitatory currents.

Neurobiological experiments have revealed three key mechanisms through which ampakine compounds can alleviate memory and cognitive impairments:

I. Ampakines enhance synaptic transmission without significant adverse effects.

II. Ampakine compounds reduce the threshold for inducing long-term potentiation (LTP), thereby improving its formation.

III. Ampakines have the ability to increase the manufacture of neurotrophic factors, especially brain-derived neurotrophic factor (BDNF) (Gümrü,2012). .

Moreover, ampakines offer potential benefits in the therapy of neurological and psychiatric disorders. First, there is evidence suggesting that ampakines can rectify impaired or inadequate glutamatergic transmission associated with conditions involving loss of consciousness. Second, ampakine compounds promote the induction of LTP through excitatory transmission. Finally, ampakine-induced excitatory stimulation can regulate the expression of neurotrophins in the cortical telencephalon. Consequently, ampakines indirectly augment the effects of neurotrophins by increasing their availability. As a result, ampakines have a profound impact on the formation, development, and differentiation of nerve cells. Additionally, ampakines are noteworthy for their indirect influence on

synapse morphology and the formation of synaptic functions. Their primary mechanism of action involves the MAPK/ERK pathway, allowing ampakine compounds to modulate gene expression, cell survival, and even apoptosis (Gümrü, 2012).

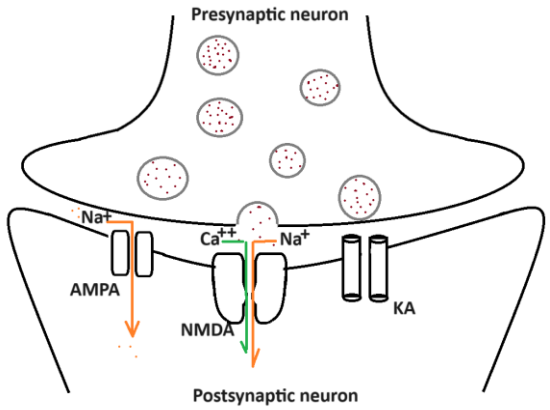

Figure 1. This figure shows the ionotropic receptor of glutamate.

2. The Classification of Ampakines

Currently, four distinct classes of AMPAKINE compounds have been identified. These classes include the following:

1- Pyrrolidine derivatives

2-Benzoylpiperidine and benzoylpyrrolidine derivatives

3- Benzothiazide derivatives

4-Biarylpropylsulfonamide derivatives (Gümrü et al, 2012)

Ampakines have profound impacts on the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). *In vivo* studies have demonstrated that the administration of various structurally diverse families of positive modulators can effectively increase the expression of BDNF and NGF. Furthermore, ampakine treatment has shown potential in reducing neural cell death in cases of excitotoxic brain injuries. Additionally, ampakines can address deficiencies in long-term potentiation (LTP) within the hippocampus. The elevation of BDNF levels is associated with enhanced neuronal survival and improved functional outcomes (Gümrü et al.,2012)

3. Properties Of New Ampakine Compound Pesampator (PF-04958242)

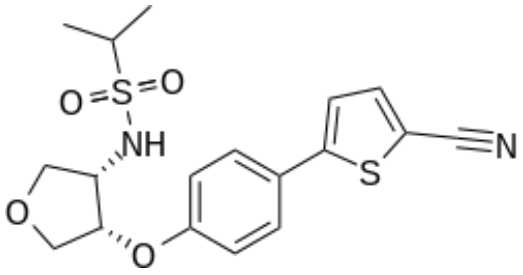

Figure 2. The Chemical Structure of PF-04958242 (Pesampator) Compound (Shaffer et al, 2015)

PF-04958242, also known as pesampator, is an ampakine compound belonging to the biarylpropylsulfonamide class. In rodent experiments, the

neuropharmacokinetic properties of this compound were evaluated following a single-dose administration. Functionally, pesampator was observed to act as a positive allosteric modulator of AMPA receptors, which are glutamate-based receptors, in primary rat cortical neurons. Notably, the Pesampator compound significantly increased AMPA-induced current by approximately fivefold compared to control conditions (Shaffer et al, 2015). Furthermore, in Sprague–Dawley rats, a single subcutaneous dose of pesampator (1 mg/kg) demonstrated similar half-life results in plasma, cerebrospinal fluid, and brain tissue. Additionally, intravenous administration of a single dose of Pesampator (0.01 mg/kg, IV) was conducted in other studies involving Sprague–Dawley rats (Shaffer et al, 2015). In some experiments, it has been noted that low doses of PF-04958242 (Pesampator) can enhance cognition and memory. However, higher doses of Pesampator have been associated with convulsions and deficits in motor coordination (Ranganathan et al, 2017).

To date, PF-04958242 (Pesampator) has undergone toxicology studies in both rats and dogs. Furthermore, it has been subject to numerous clinical trials involving healthy volunteers and individuals with age-related hearing impairment. The cognitive effects of Pesampator have been investigated in populations affected by specific neurological conditions, and its efficacy in treating cognitive impairments associated with schizophrenia has been evaluated. However, no experiments have been conducted on Alzheimer's disease using this compound (Shaffer et al, 2015, Ranganathan et al, 2017). Based on the understanding of ampakine mechanisms and considering these findings, it can be suggested that if the Pesampator compound is administered parenterally to Alzheimer's patients, it holds promising potential in the treatment of neurodegenerative disorders.

4. Properties Of Ampakine Compound Hydroflumethiazide

Figure 3. The Chemical Structure of Hydroflumethiazide Compound (Hydroflumethiazide, 2021).

Hydroflumethiazide, an ampakine compound derived from benzothiazide, possesses a trifluoromethyl group that has demonstrated a significant influence on the

binding stoichiometry to the AMPA receptor. In a study comparing benzothiazide derivatives, hydroflumethiazide was found to be the second most potent compound in terms of its effect (Ptak et al, 2009). Considering these properties, hydroflumethiazide emerges as a promising candidate to cure of Alzheimer's disease.

5. Neurotrophic Factors

The symptoms of Alzheimer's disease largely stem from the degeneration of neurons. Cortical regions of the brain are particularly affected, with significant degenerative changes observed in the cholinergic and noradrenergic systems. Additionally, the hippocampal region of the human brain is also notably impacted by the disease. Notably, there is a significant increase in the existence of neurotrophic factors within the human brain. These neurotrophic compounds primarily consist of four agents: brain-derived neurotrophic factor (BDNF), neurotrophin-4/5 (NT-4/5), nerve growth factor (NGF), and neurotrophin-3 (NT-3). Among these agents, NGF has garnered the most recognition and has been extensively studied thus far (Flynn, 1999; Hefti, 1994)

5.1. NGF and BDNF

One challenge encountered with nerve growth factor (NGF) is its deficiency to effectively cross the blood–brain barrier, limiting its accessibility to brain-derived neurotrophic factors. Furthermore, NGF (Flynn, 1999; Hefti, 1994) has shown a particular selectivity for cholinergic neurons, while noncholinergic neurons are affected in untreated Alzheimer's patients. This selectivity highlights the need for other neurotrophic factors in the treatment of Alzheimer's disease. There is evidence to suggest that noradrenergic neurons may respond to neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and neurotrophin-5 (NT-5) compared to NGF [15, 16]. Synaptic plasticity, describe as movement-based alterations in synaptic power, is a fundamental characteristic of the central nervous system. Long-term alterations in synaptic power observed during LTP and LTD are recognized as cellular machineries involved in the accumulation of memory. Therefore, the arragement of synaptic plasticity holds significant importance in the treatment of various psychiatric and neurological diseases (Kuipers, 2006).

The neurotrophin family, consisting of polypeptides such as NT-3, NT-4/5, NGF, and BDNF, performs a significance position in regulating neuronal differentiation and related processes.

Moreover, this family continues to shape the functions and structures of neural circuits during adolescence. BDNF, a neurotrophic factor, appears to be a key modulator of synaptic transmission and plasticity at excitatory synapses in adults (Kuipers, 2006). BDNF is synthesized and stored in glutamatergic neurons. During activity-dependent behavioral situations, it can be released from dendrites and axon terminals. In the hippocampus, BDNF is stored in principal neurons and is released from their dendritic terminals in response to high-frequency stimulation. Within the extracellular space, the BDNF precursor compound undergoes cleavage, resulting in the formation of mature BDNF. Mature BDNF then binds to the tyrosine kinase B receptor, that is located at both the pre- and postsynaptic regions of glutamatergic synapses (Kuipers, 2006; Hefti, 1994; Drake, 1999). Among all neurotrophins, BDNF is the only signaling system that exhibits widespread distribution throughout the adult forebrain and various hippocampal subregions.

Long-term potentiation refers to a persistent and robust augment in synaptic strength that occurs in response to high-frequency stimulation of excitatory inputs. LTP induction is closely associated with a rapid elevation of calcium levels in the postsynaptic region, which typically depends on the activation of NMDA-glutamate receptors. The initiation phase of LTP involves the covalent modification of existing proteins without the need for new gene expression. BDNF plays a modulatory role in high-frequency stimulation, acute release, LTP induction, and the maintenance of LTP. Studies focusing on the local application of BDNF propose a potential mechanism involving voltage-dependent activation of novel sodium channels. Activation of these channels brings about rapid depolarization of the cell membrane, resulting in increased calcium influx into dendritic spines (Kuipers, 2006; Aoki et al, 2000). Dendritic protein synthesis is influenced by various neurotransmitters, including glutamate and dopamine, as well as BDNF. However, the BDNF-TrkB system emerges as a distinct regulator of glutamate synapses (Kuipers, 2006). Inhibition of the BDNF-TrkB pathway impairs LTP and hippocampal-dependent memory. Additionally, chronic infusion of BDNF in the hippocampus has been shown to alleviate stress-induced damage to LTP (Kuipers, 2006; Yin, 2002; Radecki et al, 2005).

BDNF, an essential neurotrophic factor, faces the challenge of not being able to cross the blood–brain barrier directly. A promising alternative approach

for addressing this issue involves the use of positive modulators of AMPA receptors called AMPAkines. By strongly enhancing BDNF expression in the brain, AMPAkines offer potential therapeutic benefits for cognitive function disorders (Kuipers, 2006; O'Neill et al, 2004) However, a potential challenge in this therapeutic approach is the diminished effectiveness of BDNF following long-term use of AMPA. One possible solution is intermittent treatment with AMPAkines, which may induce sustained levels of BDNF. Additionally, AMPAkines have shown the ability to enhance neural proliferation in the adult hippocampus. Although the therapeutic effects of AMPA receptor modulators are still being investigated, there is promising evidence that Ampakine compounds can improve cognitive functions in both human and animal subjects (Kuipers, 2006; Lynch, 2006).

Dendritic protein synthesis is a mandatory stage for the formation and permanency of neuronal circuits and synapses in the brain. It involves three distinct stages: initiation, elongation, and release (Kuipers, 2006; Wells*,2000). Each of these stages relies on multiple factors and is regulated by various proteins, including kinases. Protein synthesis is crucial for memory formation and maintenance. For instance, inhibiting mRNA translation of proteins hinders the long-term storage and persistence of newly acquired memories and learned tasks. The regulation of dendritic protein synthesis takes place a serious situation in synaptic plasticity, particularly in events such as long-term potentiation and long-term depression. Brain-derived neurotrophic factor (BDNF) is a key player in modulating synaptic plasticity and learning processes. BDNF activates protein synthesis in neuronal cells and dendrites through stimulation of its receptor, tyrosine receptor kinase B (TrkB). This activation leads to enhanced translation through the phosphorylation of various translation factors and kinases. Examples of these factors include p70S6 kinase and initiator factor 4EBP1 (Kuipers, 2006; Takie, 2004).

5.2. Receptors of Neurotrophins

Two distinct groups of neurotrophin receptors have been identified on the cell membrane, each exhibiting different structures and activities. The first group consists of the p75NTR receptor, while the second group comprises tyrosine kinase receptors (Kayaalp, 2002). The tyrosine kinase receptor group includes TrkA, TrkB, and TrkC receptors. The $p75^{NTR}$ receptor, which belongs to the tumor

necrosis factor receptor family, is a glycoprotein. Among the three receptors in the second group, TrkA primarily binds to NGF neurotrophin, TrkB primarily binds to BDNF and NT-4/5 neurotrophins, and NT-3 neurotrophin selectively binds to TrkC (Kayaalp, 2002). Activation of these neurotrophin receptors by binding to their appropriate neurotrophin (NGF, BDNF, NT-3, and NT-4/5) leads to the activation of three distinct pathways: the Ras/MAPK pathway, PI3-K pathway, and phospholipase C-γ-1 pathway. The Ras/MAPK pathway is connected with nerve cell differentiation processes, while the PI3-K pathway is included in neuronal survival and growth processes. Activation of the PLC pathway facilitates synaptic plasticity (Kayaalp, 2002).

6. Ampakines and Consciousness Rise

Ampakine compounds, well known for their memory-enhancing effects, are specifically recognized for their ability to enhance communication both within and between cortical regions. Despite extensive laboratory studies, evidence supporting the hypothesis that they act on targets other than AMPA receptors is still lacking. Moreover, when administered peripherally, ampakines demonstrate rapid and excitatory conduction similar to that observed with direct brain infusions. In fact, ampakines have been considered the only class of agents capable of generating comparable *in vitro*/*in vivo* enhancements in excitatory postsynaptic potentials. These observations raise two significant questions (Lynch et al, 2014).

First, does the enhancement of monosynaptic transmission lead to increased throughput within a polysynaptic communication network? While it may appear as an inevitable outcome, each level within the neuronal cascade possesses local progression mechanisms that can be suppressed by the recruitment of diverse kinds of inhibitory interneurons. Inhibitory elements replies to both direct inputs and discharges of glutamatergic neurons, thereby creating intricate local connectivity networks among themselves. Consequently, it is possible to suppress excessive inputs and restore a certain level of normalcy (Lynch et al, 2014).

Second, what are the physiological results of improved network throughput assuming that the signal boost is achieved? Some studies have suggested that even subtle enhancements in monosynaptic transmission through ampakine compounds can yield greater effects at the level of the trisynaptic intrahippocampal circuit. These observations suggest that increased transmission at one junction can propagate to a larger number of cells,

reaching another site. The recurrence of most steps in response to ampakine compounds implies that the drug gains greater support for efficacy. This perspective highlights the potential for ampakine-type substances to exert significant effects on the glutamatergic neuron chains forming the cortical communication network (Lynch et al, 2014).

7. Synaptic Plasticity and Memory Condition

A significant focus of mechanism-based research on memory enhancement revolves around synaptic plasticity and the impacts of long-term potentiation (LTP). Extensive studies over the years have established that the capacity for large memory is strongly correlated with the number of connections between neurons, which serve as the encoding sites for new information. Investigations into LTP have revealed that the individual synapses within the cortical telencephalon have all the features associated with the memory substrate (Lynch et al, 2014; Bliss, 1993; Staubli, 1987). The increase in transmission strength occurs rapidly and persists for a substantial period without causing detrimental effects on the enhanced connections required for high memory capacity (Lynch et al, 2014; Rioult-Pedotti, 2000). Numerous experimental studies have approved the strong associations between LTP and various forms of memory. Moreover, LTP exhibits a close connection with the theta rhythm, which is linked to the process of learning (Lynch et al, 2014; Hasselmo, 2006). Observations suggest that drugs capable of increasing theta activity and inducing high-frequency discharge bursts may enhance learning. Examples include physostigmine, which accelerates central cholinergic conduction, increases the theta rhythm, and has shown improved learning outcomes in certain experiments. Notably, such drugs are between the few ratified therapies for Alzheimer's disease. However, cholinergic systems in the brain serve multiple functions, some of which are homeostatic, possibly explaining why targeting cholinergic mechanisms is not widely considered a viable approach (Lynch et al, 2014; Noetzli, 2013; Hosseini et al, 2001).

An alternative approach relies on theta activity and involves the occurrence of broad hyperpolarization potentials. These potentials are induced by a series of short theta bursts, which serve to stimulate long-term potentiation (LTP) in target neurons. Posthyperpolarization potentials (AHPs) occur at regular intervals during the theta sequence to counterbalance depolarization and prevent voltage-dependent synaptic

NMDA receptors from being unblocked. Calcium uptake into the cell via these receptors leads to the deliver of cations from intracellular stores and triggers a cascade of events that reinforce synaptic connections. Posthyperpolarization potentials are regulated via a series of voltage-sensitive potassium channels that respond to changes in calcium levels (Lynch et al, 2014; Monaghan et al, 2012). The identification of triggers for LTP suggests that enhancing NMDA receptor-mediated calcium influx is a viable goal for memory augmentation. The presence of numerous modulators on these receptors indicates a promising direction for the development of positive allosteric drugs (Lynch et al, 2014; Lloyd-Fox, 2010). Most of these efforts primarily aim at the treatment of neuropathological and psychiatric disorders such as schizophrenia and depression rather than memory enhancement (Lynch et al, 2014; Lloyd-Fox, 2010).

Increasing the current through AMPA receptors leads to greater postsynaptic depolarization and reduces the voltage-dependent blockade of NMDA receptors. This condition promotes the induction of LTP by amplifying AMPA receptor currents. Experimental studies in this regard have been facilitated by the discovery of AMPA receptor regulators that readily penetrate the brain and enhance rapid glutamatergic transmission (Lynch et al, 2014; Lynch, 2004). The initial positive regulators in this context are benzamide compounds. However, subsequent laboratory investigations have revealed the existence of a distinct family of compounds that decelerate the deactivation or desensitization of ligand-bound AMPA receptors, known as AMPAKINES.

8. Learning-Based Synaptic Modifications as Memory Augmentation Routes

The investigation of long-term potentiation (LTP) has significantly advanced our understanding of memory mechanisms. Early evidence obtained through electron microscopy has revealed that constant potentiation is accompanied via morphological alterations in dendritic extensions (Lynch et al, 2014; Chang, 1984). Several studies have also reported an increase in synapse size, indicating a parallel between LTP and postlearning processes (Lynch 2014; Chen et al, 2007]. From an anatomical perspective, these restructuring events suggest that induction events associated with LTP or memory formation induce significant changes in the actin cytoskeleton. Experimental findings

have demonstrated that theta firings result in a notable increase in dendritic processes containing high concentrations of polymerized actin (Lynch, 2014; Lin et al, 2005; Kramar et al, 2006). Furthermore, investigations utilizing fluorescence deconvolution tomography to assess the concentrations of active signaling proteins at individual synapses have identified numerous GTPase-initiated pathways are inclusived of the establishment and stabilization of actin filament networks following theta firing stimulation. Notably, these studies have also identified membrane receptors that regulate the cascade activity necessary for the remodeling of the actin cytoskeleton to consolidate LTP (Lynch, 2014; Rex et al, 2009; Seese et al 2012).

Brief treatments with BDNF have been shown to activate specific and robust signaling pathways that induce actin polymerization, leading to increased long-term potentiation (LTP) and theta burst activity. The effects of LTP and theta stimulation appear to be directly mediated by actin regulatory pathways during the induction phase. In particular, the disruption of extracellular BDNF impairs the stabilization of LTP triggered via theta firing stimulation (Lynch, 2014; Chen et al, 2006; Kovalchuk et al, 2002). Neurotrophic factors, therefore, play a crucial role in the normal synaptic changes associated with learning. Enhancing BDNF signaling is a potential biological approach to enhance memory, and peripheral administration of this protein may have significant central effects. Agonists targeting the TrkB receptor that can penetrate the brain have been developed, and these agonists have shown the ability to enhance brain functions in various injury conditions (Lynch 2014; Ding et al, 2013; Schmid et al, 2012).

Studies on the influence of these neurotrophic factors on memory in healthy individuals are still emerging. However, initial research suggests that acute systemic treatment may enhance objective recognition, object-place, and fear memory when administered shortly prior to the task. Additionally, memory related to object location remained improved even after a delay of 3 hours posttreatment. Another approach to studying the role of BDNF in memory is to investigate the transcription factors positively regulated by neuronal activity (Lynch 2014; Isackson et al,1991; Gall, 1992). This suggests that increasing excitatory currents toward neurons can upregulate neurotrophins, such as through the use of Ampakines. Semichronic therapy with AMPAKINEs has been shown to enhance BDNF protein levels and exert potent

effects on the brain. However, there is limited research on the upregulation of BDNF in high-functioning animals. Nonetheless, the potential of such treatments holds greater significance than merely the development of drugs. Exciting findings with upregulation and receptor agonists targeting brain diseases indicate that BDNF-dependent pathways represent one of the promising mechanisms for successful approaches to enhancing memory.

9. Dendritic Spines

Dendritic spines are tiny protrusions found on the dendritic branches of neurons (Tan, 2015; Calabrese, 2006). These spines play a crucial role in synaptic connectivity and the organization of polymerized or filamentous actin. Dendritic spines are widely distributed all around of the central nervous system, including the hippocampal and pyramidal neurons in the motor cortex, Purkinje neurons in the cerebellum, and sensory neurons in the dorsal horn of the spinal cord (Tan, 2015; Strata et al, 2000; Tan, 2012; Wolpaw, 1985). They account for more than 90% of excitatory synapses in the central nervous system (Tan, 2015; Kirov et al, 1999).

9.1. Dendritic Spines In Functions Of Synapses

Dendritic spines have garnered significant attention in the study of learning and memory. One well-established aspect of the neural basis of learning and memory is long-term potentiation (LTP) (Tan, 2015; Malenka, 2003). LTP refers to the long-lasting enhancement of synaptic strength following synchronous activity. *In vitro* studies have shown that the increased synaptic activity induced by LTP can persist for an extended period. Similarly, *in vivo* observations have demonstrated that LTP can last for days. Most studies on LTP have been conducted in the hippocampus or cortex. LTP is characterized by an early phase and a late phase. The early phase of LTP is rapid and does not require protein synthesis, typically occurring within 60 minutes of induction in hippocampal slice experiments. The early phase is associated with posttranslational modifications of excitatory glutamatergic AMPA receptors (Tan 2015; Frey, 2008). The passage from the early phase to the late phase of LTP comprises the actuation of protein kinase A, protein kinase C, and extracellular signal-related kinase, which are members of the mitogen-activated protein kinase family. Activation of these molecular pathways finally leads to gene transcription and protein synthesis, which

are essential for the late phase of LTP (Tan, 2015; Ackermann, 2003;Bramham, 2008; Impey et al,1998; Matsuzaki et al, 2004).

Actin polymerization and stabilization in dendritic spines are crucial for enhancing synaptic efficacy. Inhibiting actin polymerization using latrunculins or cytochalazin interferes with the late phase of LTP and the maturation of dendritic spines (Tan, 2015; Fischer et al, 1998). The neurotrophin BDNF has been shown to be involved in the translation patterns related to long-term memory and contributes to the improving of dendritic spines (Tan, 2015; Lu, 2008). Calcium entry through activated NMDA receptors increases intracellular calcium, which is essential for LTP stimulation. Several features of dendritic spines contribute to the regulation of calcium signaling. First, due to their narrow dimensions, dendritic spines act as diffusion barriers for calcium ions. Second, the spine neck creates electrical resistance across synaptic transmission. Third, despite being partially insulated from dendritic branches, bidirectional current flow can occur, establishing an electrical connection between the spine and the dendritic branch. The morphology of dendritic spines plays a vital role in modulating synaptic function (Tan, 2015; Lu, 2008). Larger, mushroom-shaped dendritic spines are connected with stronger synapses and the formation of memory (Tan 2015; Fifkova 1985). The neck region of dendritic spines treats as a diffusion barrier, controlling the actions of cations and other molecules. This region directly affects local function by regulating the passage of cations and molecules. By changing their shapes, dendritic spines can open or close diffusion gateways in response to activity. Thus, the structure of dendritic spines significantly influences the intracellular functions of synapses. By slowing down the diffusion of calcium ions, dendritic spines conduce to the localized gathering of calcium and help sustain an enhanced level of calcium ions over an extended period (Tan 2015; Bourne, 2007; Araya, 2006; Majewska, 2000; Majewska, 2000; Halpain, 2005).

9.2. Pathologies and Dendritic Spines

Dysfunctions in dendritic spines are associated with a range of disorders. Neurodegenerative conditions and chronic substance abuse have been linked to abnormal dendritic spines (Tan, 2015; Halpain, 2005]. In individuals with intellectual disabilities and in animal models, dendritic spines appear smaller and weaker than those in normal individuals. The abnormal state of dendritic spines is indicative of synaptic

dysfunction, as mental retardation is often associated with genetic mutations affecting structural proteins crucial for maintaining synaptic integrity.

9.3. The Role of Dendritic Spines in the Existence of Memory

Dendritic spines have a crucial role in the exchange of biochemical and ionic signals during excitatory synaptic transmission. The dynamic nature of dendritic spines observed in both laboratory and living organisms suggests that changes in their shape and number contribute to the evolution and retention of memory (Chapleau et al, 2009; Dunaevsky et al, 1999; Mizrahi et al, 2004; Yuste, 2001; Ethell, 2005). Numerous studies have demonstrated that alterations in spine structure or density, following the stimulation of synaptic plasticity, underlie the cellular machineries of associative learning and memory (Chapleau et al, 2009; Segal, 2005). The morphology of dendritic spines is believed to be closely linked to their functional properties. Spines are broadly categorized into three main types: stubby-shaped, mushroom-shaped, and thin-shaped (Matsuzaki, 2004; Majewska, 2000).

Mature dendritic spines are thought to develop from dendritic filopodia, which are long and thin protrusions originating from the dendrite. These structures then initiate spinogenesis and synaptogenesis with axons. Recent research has revealed that dendritic spine morphology influences the entry and diffusion of calcium ions, which in turn affect the overall dendritic structure (Chapleau et al, 2009; Peters, 1970; Korkotian, 2004; Noguchi et al,2005). Furthermore, there is evidence that dendritic spine density and morphology can change in response to environmental stimuli and learning experiences *in vivo*, as observed in studies conducted on rats and mice. These findings also indicate that molecular composition changes occur within dendritic spines during the learning process (Chapleau et al, 2009; Cohen-cory et al, 2010).

9.4. BDNF and Regulation of Dendritic Spines

Both BDNF and TrkB are members of the nerve cell growth factor family and play crucial roles in regulating synaptic plasticity and CNS development. Experimental evidence has confirmed that BDNF is essential for maintaining dendritic spines in the adult CNS (Vigers et al, 2012; Kiprianova et al, 1999). Additionally, the induction of long-term potentiation (LTP), which involves changes in dendritic spine strength, relies on the presence of BDNF. The plasticity of

dendritic spines encompasses the production of new spines and the transformation of thin filopodial protrusions into more complex structures. This developmental process heavily relies on the mobilization of various proteins, particularly actin, which is abundantly present in dendritic spines. Actin-related proteins also play a role in postsynaptic events (Ziv, 1996; Penzes, 2012; Tyler, 2001).

The BDNF-TrkB complex, when activated, can influence signal propagation, dendritic spine density, and synapse formation in cortical and hippocampal neurons. Specifically, this complex has been shown to develop dendritic spine intensity in the apical dendrites of CA1 pyramidal cells (Tyler, 2001). Studies by Tyler and Pozzo-Miller have revealed that BDNF can induce changes in spine morphology in hippocampal tissue culture, promoting the formation of thin- and mushroom-shaped spines. It has been suggested that thin spines have a "learning function" due to their high susceptibility to changes in response to neuronal activity, while the more stable mushroom-shaped spines are associated with a "memory function." BDNF not only increases spine density but also influences the structural characteristics of spines, promoting both the "learning" (thin-shaped) and "memory" (mushroom-shaped) properties (Tyler, 2001).

Conclusion and future prospects

This article discusses the relationship between ampakine compounds and neurotrophic factors, highlighting their potential impact on memory and synaptic connections. This suggests that the combination of increased synapse formation and the influence of neurotrophic factors can enhance memory processes.

AMPA receptors are composed of four subunits and GluA2 prevents the open channel from Ca conductance, while only GluA1 and GluA3 subunit-containing AMPA receptors allow Ca passage. When AMPA receptors are activated by glutamate, Na ions flow through receptors and depolarization occurs. If activation of AMPA receptors increases, the depolarization gets a high level and then NMDA receptors can be activated. Activation of NMDA receptors can be explained by releasing of Mg ion from the NMDA receptor channel. We can say that Ca ion is one of the basic induction factor of LTP (Kayaalp, 2002).

After high amounts of Ca increase in neuron, Ca-calmodulin complex occurs. This complex activates Adenylate cyclase and cAMP levels increase. After PKA

activation, formation of CREB becomes active. CREB activates CRE and then CRE increases BDNF formation by gene expression. After these events, neuroprotection, neural plasticity and synaptogenesis degree elevate (Impey et al, 1998). So it can be suggested that AMPAKINE compounds can perform a connection network between stimulation of the AMPA receptors and Neuroprotection.

It is believed that Late phase LTP is basic thing of long-term-memory. Duration in Late phase LTP changes between hours and days. In late phase LTP, expression of necessary proteins occurs. These proteins makes the neurocommunications stronger. Deficits in transmission strength within the cortex probably contribute to the cognitive impairments associated with aging and various neuropsychiatric diseases. Ampakine compounds augment neuronal transmission, without causing noticeable side-effects, and because of this reason we can propose that they can be plausible treatments for cognitive impairments (Lynch, 2004).

The article emphasizes the role of ampakine compounds in promoting the development and strengthening of actin structures in neurons, which further supports the strengthening of synaptic connections.

The mechanism of action of ampakine compounds holds promise in addressing the challenging issues associated with Alzheimer's disease treatment. Understanding the importance of neurotrophic factors in disease management becomes apparent in this context. By identifying the most effective treatment approaches through these methods, unnecessary financial costs and associated economic losses can be minimizedg. Furthermore, the adoption of effective treatments can help prevent health complications and reduce the occurrence of side effects that pose risks to human well-being. Consequently, various ampakine compounds, such as pesampator and hydroflumetazide, may be favorable options for treating Alzheimer's disease, offering new hope for addressing memory loss through enhanced synaptogenesis.

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