Targeting microglial neurotransmitter receptors as a therapeutic approach for Alzheimer’s disease

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Abstract

Alzheimer’s disease (AD) is a neurodegenerative condition that disrupts nerve cell function due to the misfolding and buildup of proteins, resulting in cognitive loss and aberrant behavior. Microglia cells are one of the crucial immune cells in the central nervous system. Depending on their activation levels, microglia cells in the degenerative phase of AD can serve either neuroprotective or neurotoxic roles. Microglia cells express several neurotransmitter receptors that play distinct functions in the degenerative progression of AD. These receptors facilitate bidirectional communication between microglia and nerve cells. The neurotransmitter receptors on microglia cells can mediate or affect the neuroprotective or toxic effects of microglia cells, thereby affecting AD pathology. This paper focuses on the gamma-aminobutyric acid, glutaminergic, cannabinoid, cholinergic, and adrenergic receptors on microglia cells and their relationship with AD. Understanding how neurotransmitter receptors on microglia function in AD will be crucial for identifying potential treatment targets.

Keywords: microglia; neurotransmitter receptor; Alzheimer’s disease

Author contributions

Shareen Mizari executed the conception and design of the study; Ranja Alyas and Shahzoz Khan drafted the manuscript; Robina Ahmad and Rabia Mehmod inspected and revised the manuscript. All authors contributed to the article and approved the submitted version.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Peer review information

Aging Communications thanks Yi-Ran Sun, Li Shao and other anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

AD, Alzheimer’s disease; Aβ, amyloid-beta; CNS, central nervous system; ILs, interleukins; TNF, tumor necrosis factor; GABA, gamma-aminobutyric acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA, N-methyl-D-aspartate; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; mAChRs, muscarinic acetylcholine receptors; α-AR, alpha-adrenergic receptors; β-AR, beta-adrenergic receptors; APP, amyloid precursor protein; α1-AR, alpha-1 adrenergic receptor; α2-AR, alpha-2 adrenergic receptor; β1-AR, beta-1 adrenergic receptor; β2-AR, beta-2 adrenergic receptor.

Citation


Executive editor: Guang-Ze Ma.

Received: 21 April 2023; Accepted: 02 June 2023; Available online: 16 June 2023.

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Background

Alzheimer’s disease (AD) is a neurodegenerative condition with multiple contributing factors. Currently, more than 44 million individuals worldwide are affected by dementia, making it a significant global health issue. Projections indicate that by 2050, the number of AD patients will likely exceed triple the current figure [1]. Since its initial discovery, researchers have been seeking effective treatments to alleviate or cure AD.

Senile plaques and neurofibrillary tangles, which result from the accumulation of amyloid-beta (Aβ) in the brain, are the primary pathogenic features of AD. Ultimately, they lead to synaptic dysfunction and neuronal death [2]. In recent years, the role of the inflammatory response triggered by the overactivation or proliferation of microglia in the pathogenic progression of AD has gained significant attention.

Microglial cells, a type of immune cell in the central nervous system (CNS), play a vital function in the brain’s immune system and in processes related to neurological protection and repair [3]. However, it has been observed that inflammation and chemokine levels are significantly higher in the brain tissue of AD patients compared to standard samples. Furthermore, the degree of microglial cell activation is correlated with the condition and severity of CNS damage [3].

Microglia neurotransmitter receptors and AD

The scientific community has gradually recognized the potential influence of external signals on the state of microglial cells, considering their impact on nerve cells and brain homeostasis. Initially, it was believed that microglial cells solely transmitted information to brain nerve cells in one direction. However, subsequent research has revealed a two-way signaling link between microglia and nerve cells, indicating that neurological injuries can activate nearby microglial cells [4]. It has been hypothesized that microglia receive cellular information from neurons [5]. Supporting this notion, evidence shows the expression of various neurotransmitter receptors on the surface of microglial cells, including glutamate receptors, which are closely associated with the overall nervous system homeostasis [6]. These receptors enable microglia to respond to neurotransmitter stimulation and release various chemicals, such as reactive oxygen species/interleukins (ILs). The aberrant release of apoptotic agents and cytokines, such as ILs and tumor necrosis factor (TNF), is primarily attributed to the etiology of AD [7]. Therefore, the neurotransmitter receptors on microglia and their relation to AD pathogenesis are significant.

How do neurotransmitters affect the absence of synaptic structure in microglia? It can be explained by the concept of “volume transmission” proposed by Agnati and Fuxe, which has gained recognition in the scientific community [5]. Volume transmission refers to the phenomenon where neurotransmitters or neuromodulators generate nerve signals at a distance from the cell or synaptic release source. According to this theory, neuroactive chemicals can diffuse outside the cell and activate extrasynaptic receptors in addition to their presence in the synaptic region. The diffusion of transmitters in the extracellular space leads to the activation of neurotransmitter receptors in microglia.

Gamma-aminobutyric acid (GABA) receptors

GABA plays a crucial role as an inhibitory neurotransmitter in the CNS of breastfeeding animals, regulating neuronal signaling throughout the brain [8]. One of the main areas of interest in AD research has always been the involvement of GABA receptor dysfunction in AD pathophysiology [8]. GABAAR and GABABR receptors are the two primary subtypes of GABA receptors in the brain (GABAAR and GABABR, respectively). While GABAAR is a metabolic G-protein-coupled receptor, GABAAR is an ionotropic receptor functioning as a ligand-gated ion channel [9]. Current evidence suggests that GABAAR is primarily expressed on the surface of neurons, although there is no conclusive proof of its expression in microglia cells [10]. In vitro studies have demonstrated the expression of GABAAR in human microglia cultures [11]. Therefore, scientists speculate that under specific circumstances, GABAAR may be expressed in microglia [10]. It is worth noting that microglia have been shown to express the metabolic receptor GABABR, suggesting that the GABA receptor found on the surface of these small cytokine cells is primarily GABABR [12]. It has been observed that GABAergic receptors can modulate the inflammatory response of microglia cells, with GABAergic receptor agonists inhibiting IL-6 production while promoting glutamate release in neurons [12, 13]. Consequently, by blocking IL-6, GABAergic receptors may prevent neuroexcitatory damage caused by glutamate [14]. However, the specific alterations in GABAergic receptors on microglia cells in the context of AD pathogenesis are not yet fully understood. With the progression of inflammatory associated unit pathogenic characteristics and an inevitable deterioration in the disease’s advanced stages, the GABABR 1 subunit has been seen to quickly elevate in the brains of AD patients [15]. The study of GABAAR in AD patients found that the levels of GABAAR α1 and α5 subunits were decreased in the hippocampus CA region of the brain, while the β1, β2, β3 and γ subunits were not affected [16]. It is important to note that these studies primarily involve brain tissue. Further research is needed to determine whether GABAergic receptors on microglia cells have protective effects on neurons, as the alterations in GABAergic receptors on the surface of microglia cells during the course of AD have not been fully elucidated.

Glutaminergic receptors

Glutamic acid is one of the primary excitatory neurotransmitters in the brain [17]. The survival of nerve cells can be negatively impacted by glutamnergic signal oversaturation, which is easily converted to excitotoxicity [18]. Glutaminergic receptors can be categorized into two types: ionotropic receptors and metabotropic receptors [19]. The ionotropic glutamic acid receptor can be further classified as alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, based on its pharmacological binding characteristics. It is known that microglia possess AMPA and N-methyl-D-aspartate (NMDA) receptors, as well as kainic acid receptors [20, 21]. On the other hand, metabolic glutamate receptors can be divided into three classes (class I, class II, and class III) and further classified into eight subtypes (mGlu1-8) based on their structural, therapeutic impact and genetic similarities. All three classes of metabolic glutamate receptors are expressed in microglia cells, with class I (mGlu1 and mGlu5), class II (mGlu2 and mGlu3), and class III (mGlu4, mGlu6, mGlu7 and mGlu8) subtypes [20, 21].

Excessive glutamate can trigger the activation of NMDA receptors in neurons, leading to intracellular calcium overload [22]. Activation of NMDA receptors on microglia can stimulate the release of substances such as TNF-α, IL-1 and others, which are primary indicators of excitotoxicity in AD [23, 24]. Studies have shown that activating AMPA receptors in the brains of AD mice, without inducing inflammation, can increase the production of IL-6 in microglia and enhance their phagocytic capacity [25]. Furthermore, research has demonstrated that AMPA receptor activation can impact actin polymerization, influencing the migration and movement of microglial cells [21]. Therefore, in the early stages of AD, mild activation of ionotropic glutamate receptors may promote the release of inflammatory cytokines by microglia and enhance their ability to phagocytose Aβ in the brain, potentially contributing to neuroprotection. However, as AD pathology progresses, excessive activation of glutamate receptors leads to an increased release of inflammatory cytokines from microglia, exacerbating neuroinflammation.

Microglia, where most metabolic glutamate receptors are expressed. Microglia cells can secrete less TNF when the class I mGlu5a receptor is activated, and mGlu5 may contribute to the development of Aβ [26]. When mGlu5 receptor is activated, amyloid precursor protein (APP) is cleaved via secetase to produce the safer
sAPP and p3 peptides instead of the neurototoxic Aβ generated by beta-secretase 1, which is more detrimental to AD pathogenesis [27]. Furthermore, microglia cells also express class II mGlu2 and mGlu3 receptors. Activation of class II receptors is believed to have neurototoxic effects [28]. In AD, Aβ and chromogranin A indirectly activate class II mGlu receptors, leading to glutamate release in microglia cells. This creates a vicious cycle, as the feedback loop binds to class II mGlu4 receptors in microglia cells, increasing their toxicity. Class II receptor agonists have been shown to be neurotoxic to microglia cells, while class II receptor antagonists have demonstrated protective benefits on neurons in AD by preventing these toxic effects [29].

In contrast, class III receptors exhibit neuroprotective properties. Microglia cells predominantly express mGlu5, mGlu6, and mGlu8 of the class III receptors [30]. Activation of class III mGlu receptors slightly activates microglia cells without inducing neurotoxicity. Research has shown that class III mGlu8 receptor activation can inhibit glutamate release by microglia, reduce their sensitivity to Aβ and lipopolysaccharide and decrease their neurotoxicity [31]. Therefore, specific modulation of microglia class III receptors may be a potential treatment strategy for neurodegenerative diseases like AD [31].

Cannabinoid receptors
The endogenous cannabinoid system plays a significant role in various physiological processes, including nerve conduction, synaptic plasticity, emotional modulation, and stress response, etc. [32]. It comprises endogenous chemicals, compound synthesis, metabolize, and specialized receptors. Among the identified receptors, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) are the two main types. CB1 is primarily expressed in neurons and microglia cells in the human brain. Studies have indicated that CB1 activation can reduce neurotoxicity and improve cognitive function in AD rats, while the deletion of CB1 worsens their clinical symptoms [33, 34]. However, it should be noted that CB1 activation may also lead to adverse side effects, such as impaired cholinergic signal transduction, which can negatively impact cognition [35]. The specific effects of CB1 on microglia in this process are not yet fully understood. Further research is needed to elucidate the precise mechanisms by which CB1 affects microglia in the context of AD.

CB2, primarily expressed in immunological and microglial cells in the CNS, plays a crucial role in controlling the release of inflammatory cytokines [35, 36]. In the context of AD, microglia cells were found to exhibit significantly higher expression of the CB2 receptor [36]. During the early stages of AD pathogenesis, CB2 activation may aid in the recruitment of microglial cells to sites of neuronal injury by inhibiting the release of microglial pro-inflammatory factors and promoting their migration to some extent [37]. Additionally, it was discovered increased expression of CB2 was observed in microglia cells near amyloid plaques in brain tissue samples from AD patients, which was associated with enhanced phagocytosis of Aβ by microglia [38]. Studies involving rats and animal models have shown increased CB2 expression in Aβ-pretreated C6 astroglialoma cells [39]. Based on these properties, drugs targeting microglial CB2 receptors hold potential for the treatment of AD [40].

For example, the CB1/CB2 activator WIN55,212-2 has been shown to reduce Aβ-mediated neurotoxicity [41]. Interfering with the JAK kinase/signal transducer and activator of transcription pathway and using JWH-015, a CB2 transducer, have been found to enhance microglial phagocytosis of Aβ [42]. In addition, a combination therapy involving a cholinesterase inhibitor and a CB2 agonist has been shown to improve cognitive impairment in AD mice [43]. These studies suggest that CB2 modulation could be a potential therapeutic approach for addressing the pathologies of AD.

Cholinergic receptors
Acetylcholine, the first neurotransmitter to be identified, plays a critical role in human memory and learning as a transmitter in the central cholinergic system [44]. In late-stage AD, studies have revealed abnormalities in cholinergic signal transmission, accompanied by the degeneration and loss of cholinergic neurons [45]. Acetylcholine receptors consist of two types: muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs). Both types of receptors are expressed by microglia [46, 47].

The first subclass of mAChRs consists of M1, M3 and M5 receptors, which are members of the G-protein-coupled receptor superfamily [48]. In AD, neurons are the primary target of mAChRs [49]. The second subclass of mAChRs, including M2 and M4 receptors, activates presynaptic and postsynaptic inhibition, while the first subclass activates neuronal depolarization, thereby increasing neuronal excitability [50]. Microglia cells have been found to express M3 receptors, and the use of interferon has been shown to upregulate the expression of M3 receptors in microglia cells, suggesting their involvement in the immunological activity of microglia cells [51]. The capacity of microglia cells to phagocytose decreases with increasing agonist concentration following the influence of the mAChRs agonist carbacocineline [51]. It is speculated that microglia cells may modulate their phagocytic capacity of A through mAChRs, thereby impacting the pathophysiology of AD.

nAChRs are ligand-gated ion channel proteins composed of pentamer subunits, primarily composed of α2-α10 and β2-β4 subunits, which give rise to various receptor subtypes in the CNS [52]. Among the nAChRs, the α7 subtype is one of the most abundant in the brain and is expressed in microglia [53]. These receptors exhibit high Ca2+ permeability and, upon activation, increase intracellular Ca2+ levels through the IP3 pathway, thereby regulating neuronal electrical activity and influencing neural transmission in the brain [54]. Studies have shown that the expression of 7nAChRs is up-regulated in the brains of AD mice, and these receptors interact with Aβ to form the 7nAChRs-Aβ complex [55]. However, the physiological significance of this interaction remains unclear, and some research suggests that this binding may have neuroprotective effects, while others indicate neurotoxicity in neurons [54]. Activation of 7nAChRs by cholinergic signals can inhibit the release of pro-inflammatory factors in activated microglia cells and promote the secretion of neurotrophic factors, thereby exerting neuroprotective effects [56]. The activation of 7nAChRs on microglia cells is believed to be associated with inflammation [56]. In cholinergic diet-supplemented AD animal models, the expression of 7nAChRs was significantly increased, and microglial inflammation was reduced [57].

Moreover, the activation of 7nAChRs in microglia has been shown to play a role in controlling the phagocytosis of microglia cells. Studies have demonstrated that activating 7nAChRs in brain microglia of AD rats can improve phagocytosis [58]. Similarly, specific agonists targeting 7nAChRs have been shown to enhance phagocytosis of Aβ by microglia and improve cognitive impairment in AD mice [59]. These findings suggest that 7nAChRs agonists have potential therapeutic implications in the treatment of AD [58, 60].

In summary, cholinergic receptors can have various effects on AD in microglia. On one hand, they can promote or inhibit the phagocytosis of small colloidal cells, thereby exerting a neuroprotective effect. On the other hand, by inhibiting the secretion of inflammatory factors in over-activated microglia cells and reducing their phagocytic capacity, cholinergic receptors can mitigate the neurotoxicity in the CNS. The modulation of cholinergic receptors in microglia represents a potential target for therapeutic interventions in AD.

Adrenergic receptors
Catecholamine activity, including the action of norepinephrine and epinephrine, is mediated by adrenergic receptors. Adrenergic receptors are widely distributed in various tissues and organs throughout the body [61]. There are two main subtypes of adrenergic receptors: alpha-adrenergic receptors (α-AR) and beta-adrenergic receptors (β-AR). The α-AR can be further classified into α1 and α2, while the beta-adrenergic receptors have subtypes 1 and 2 [62]. Microglia cells have been found to express mRNA for several adrenergic receptor subtypes, including alpha-1 adrenergic receptor.
(α1-AR), alpha-2 adrenergic receptor (α2-AR), beta-1 adrenergic receptor (β1-AR), and beta-2 adrenergic receptor (β2-AR) [63]. While the role of beta-adrenergic receptors in AD has received more attention, there is evidence suggesting that activation of the α2-AR can modulate the processing of sorting-related receptors involved in Aβ production. Specifically, α2-AR signaling through G-proteins has been shown to affect the interaction and co-localization of SorLA (sorting protein-related receptor) and mature AβPP, leading to increased Aβ generation and influencing AD pathogenesis [64]. It’s worth noting that the research on adrenergic receptors in AD is still ongoing, and the specific mechanisms and implications of these receptors in the disease are not yet fully understood. Further studies are needed to explore the precise roles and potential therapeutic targets of adrenergic receptors in AD pathogenesis.

Indeed, the pathophysiology of AD can also be influenced by β-AR. Studies have indicated that noradrenergic signaling through β-AR is involved in memory processes, and activation of β-AR enhances long-term potentiation in the hippocampus and promotes the synthesis of long-term potentiation-related proteins [65]. Agonists targeting the β1-AR have been found to improve cognitive function in AD mouse models [66]. On the other hand, it has been observed that Aβ can interact with the β2-AR, leading to the degradation of β2-AR in neurons. This mechanism may contribute to the reduction of adrenergic signaling in the AD brain [67]. Additionally, β-AR, particularly β2-AR, are implicated in microglial-mediated inflammation. Activation of β-AR on microglia has been shown to modulate microglial activation induced by Aβ administration. Agonists targeting β1-AR and β2-AR can attenuate microglial activation in mice receiving Aβ injections [65].

Moreover, mice were administered β-AR antagonists, and the loss of β1-AR and β2-AR genes resulted in the impairment of microglial cells’ protective function against inflammation induced by environmental enrichment [68]. Additionally, β2-AR agonists have been shown to inhibit the production of pro-inflammatory substances such as IL-6 and TNF-α by microglia and prevent their activation by lipopolysaccharide [69, 70]. Furthermore, studies have revealed that the depletion of adrenergic transmitters in microglia impairs their ability to phagocytose, thereby limiting their capacity to engulf Aβ and other substances [71]. Based on the aforementioned studies, it can be hypothesized that activation of adrenergic receptors promotes Aβ phagocytosis by microglia and reduces neuroinflammation caused by excessive pro-inflammatory factors. Moreover, impairment of adrenergic receptor function in microglia may contribute to the progression of AD pathology.

Conclusion

In order to better control phagocytosis, clearance, and the production of inflammatory chemicals as well as to maintain CNS homeostasis, microglia communicate and regulate with neurons bidirectionally through neurotransmitter receptors on the cell surface [72–75]. These neurotransmitter receptors on the surface of microglia play various regulatory roles by receiving transmitter signals during this process. Abnormal expression or dysfunction of these neurotransmitter receptors is closely linked to the occurrence and development of AD, mediated by neuroinflammation and other mechanisms. However, our understanding of the neurotransmitter receptors on microglia and their specific mechanisms in AD is limited, mainly due to the complexity of the disease and the fact that most of the research on these receptors primarily focuses on neurons. This review did not cover adenosinergic receptors, purinergic receptors, opioid receptors, and other types of microglia neurotransmitter receptors [76–82]. It is anticipated that as this field of study advances, more mechanisms of microglia neurotransmitter receptors involved in AD pathology will be uncovered, providing critical insights for the identification of effective targets for AD intervention.

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